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(54) DIMER-SELECTIVE RXR MODULATORS AND METHODS FOR THEIR USE

DIMER-SELEKTIVE RXR MODULATOREN UND VERFAHREN ZU IHRER VERWENDUNG

MODULATEURS RXR SELECTIFS POUR LES DIMERES ET LEURS METHODES D'UTILISATION

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Description

[0001] The present invention relates to compounds having agonist, partial agonist and antagonist activity for retinoid X receptors, and to methods for the production and therapeutic use of such compounds.

Background of the Invention

[0002] The vitamin A metabolite, retinoic acid, has long been recognized to induce a broad spectrum of biological effects. For example, retinoic acid-containing products, such as Retin-A® and Accutane®, have found utility as therapeutic agents for the treatment of various pathological conditions. In addition, a variety of structural analogues of retinoic acid have been synthesized that also have been found to be bioactive. Many of these synthetic retinoids have been found to mimic many of the pharmacological actions of retinoic acid, and thus have therapeutic potential for the treatment of numerous disease states.

[0003] Medical professionals have become very interested in the therapeutic applications of retinoids. Among their uses approved by the FDA is the treatment of severe forms of acne and psoriasis. A large body of evidence also exists that these compounds can be used to arrest and, to an extent, reverse the effects of skin damage arising from prolonged exposure to the sun. Other evidence exists that these compounds have clear effects on cellular proliferation, differentiation and programmed cell death (apoptosis), and thus, may be useful in the treatment and prevention of a variety of cancerous and pre-cancerous conditions, such as acute promyleocytic leukemia (APL), epithelial cancers, squamous cell carcinomas, including cervical and skin cancers and renal cell carcinoma. Furthermore, retinoids may have beneficial activity in treating and preventing diseases of the eye, cardiovascular disease and other skin disorders.

[0004] Major insight into the molecular mechanism of retinoic acid signal transduction was gained in 1988, when a member of the steroid/thyroid hormone intracellular receptor superfamily was shown to transduce a retinoic acid signal. Giguere et al., *Nature,* 330:624-29 (1987); Petkovich *et al., Nature,* 330: 444-50 (1987); for review, See Evans, *Science,* 240:889-95 (1988). It is now known that retinoids regulate the activity of two distinct intracellular receptor subfamilies; the Retinoic Acid Receptors (RARs) and the Retinoid X Receptors (RXRs), including their subtypes, RARα, β, γ and RXRα, β, γ. All-*trans*-retinoic acid (ATRA) is an endogenous low-molecular-weight ligand which modulates the transcriptional activity of the RARs, while 9-*cis* retinoic acid (*9-cis*) is the endogenous ligand for the RXRs. Heyman *et al.*, *Cell*, 68:397-406 (1992) and Levin *et al. Nature,* 355:359-61 (1992).

[0005] Although both the RARs and RXRs respond to ATRA *in vivo*, due to the *in vivo* conversion of some of the ATRA to 9-*cis*, the receptors differ in several important aspects. First, the RARs and RXRs are significantly divergent in primary structure (*e.g.*, the ligand binding domains of RARα and RXRα have only approximately 30% amino acid identity). These structural differences are reflected in the different relative degrees of responsiveness of RARs and RXRs to various vitamin A metabolites and synthetic retinoids. In addition, distinctly different patterns of tissue distribution are seen for RARs and RXRs. For example, RXRα mRNA is expressed at high levels in the visceral tissues, e. g., liver, kidney, lung, muscle and intestine, while RARα mRNA is not. Finally, the RARs and RXRs have different target gene specificity. In this regard, RARs and RXRs regulate transcription by binding to response elements in target genes that generally consist of two direct repeat half-sites of the consensus sequence AGGTCA. RAR:RXR heterodimers activate transcription ligand by binding to direct repeats spaced by five base pairs (a DR5) or by two base pairs (a DR2). However, RXR:RXR homodimers bind to a direct repeat with a spacing of one nucleotide (a DR1). See Mangelsdorf et al., "The Retinoid Receptors" in The Retinoids: Biology. Chemistry and Medicine, M.B. Sporn, A.B. Roberts and D.S. Goodman, Eds., Raven Press, New York, New York, Second Addition (1994). For example, response elements have been identified in the cellular retinal binding protein type II (CRBPII), which consists of a DR1, and Apolipoprotein AI genes which confer responsiveness to RXR, but not RAR. Further, RAR has also been recently shown to repress RXR-mediated activation through the CRBPII RXR response element (Manglesdorf *et al., Cell,* 66:555-61(1991)). Also, RAR specific target genes have recently been identified, including target genes specific for RARβ (e.g. βRE), which consists of a DR5. These data indicate that two retinoic acid responsive pathways are not simply redundant, but instead manifest a complex interplay.

[0006] RXR agonists in the context of an RXR:RXR homodimer display unique transcriptional activity in contrast to the activity of the same compounds through an RXR heterodimer. Activation of a RXR homodimer is a ligand dependent event, i.e., the RXR agonist must be present to bring about the activation of the RXR homodimer. In contrast, RXR working through a heterodimer (e.g., RXR:RAR, RXR:VDR) is often the silent partner, i.e., no RXR agonist will activate the RXR-containing heterodimer without the corresponding ligand for the heterodimeric partner. However, for other heterodimers, (e.g., PPAR:RXR) a ligand for either or both of the heterodimer partners can activate the heterodimeric complex. Furthermore, in some instances, the presence of both an RXR agonist and the agonist for the other heterodimeric partner (*e.g.*, gemfibrizol for PPARα and TTNPB for RARα) leads to at least an additive, and often a synergistic enhancement of the activation pathway of the other IR of the heterodimer pair (e.g., the PPARα pathway). See e.g., PCT Application No. PCT/US93110204, filed October 22, 1993, published as PCT Publication No. WO 94/15902

on July 21, 1994; R. Mukherjee et al., 51 J. Steroid Biochem. Molec. Biol., 157-166 (1994) and L. Jow and R. Mukherjee, 270 Journ. Biol. Chem., 3836-3840 (1995).

[0007] RAR and RXR retinoid agonists, including both RAR specific and RXR specific agonists have been previously identified. See e.g., PCT Publication Nos. WO 94/15902 WO93/21146, WO94/15901 WO94/12880, WO94/17796, WO94/20093, WO96/05165 and PCT Application No. PCT/US93/10166; EPO Patent Application Nos. 87110303.2, 87309681.2 and EP 0718285; U.S. Patent Nos. 4,193,931, 4,539,134, 4,801,733, 4,831,052, 4,833,240, 4,874,747, 4,879,284, 4,898,864, 4,925,979, 5,004,730, 5,124,473. 5,198,567, 5,391,569 and Re 33,533; and H. Kagechika et al., "Retinobenzoic Acids. 2. Structure-Activity Relationship of Chalcone-4-carboxylic Acids and Flavone-4'-carboxylic Acids", 32 *J. Med. Chem.,* 834 (1989); H. Kagechika et al., "Retinobenzoic Acids. 3. Structure-Activity Relationships of Retinoidal Azobenzene-4-carboxylic Acids and Stilbene-4-carboxylic Acids", 32 *J. Med. Chem.*, 1098 (1989); H. Kagechika et al., "Retinobenzoic Acids. 4. Conformation of Aromatic Amides with Retinoidal Activity. Importance of *trans*-Amide Structure for the Activity", 32 *J. Med. Chem.*, 2292 *(1989);* M. Boehm et al., 37 *J. Med. Chem., 2930 (1994)*; M. Boehm et al., 38 *J. Med. Chem.*, 3146 (1995); E. Allegretto et al., *270 Journal of Biol. Chem.,* 23906 (1995); R. Bissonnette et al., 15 *Mol. & Cellular Bio.*, 5576 (1995); R. Beard et al., 38 *J. Med. Chem.,* 2820 (1995) and M.I. Dawson et al., "Effect of Structural Modifications in the C7-C11 Region of the Retinoid Skeleton on Biological Activity in a Series of Aromatic Retinoids", 32 *J. Med. Chem.,* 1504 (1989). Further, antagonists to the RAR subfamily of receptors have recently been identified. See e.g., C. Apfel et al., 89 Proc. Natl. Acad. Sci., 7129 (1992); S. Keidel et al., 14 Mol. Cell. Biol., 287 (1994); S. Kaneko et al., 1 Med. Chem. Res., 220 (1991); L. Eyrolles et al., 2 Med. Chem. Res., 361 (1992); J. Eyrolles et al., 37 J. Med. Chem., 1508 (1994); M-O Lee et al., 91 Proc. Natl. Acad. Sci., 5632 (1994); Yoshimura et al., 38 J. Med. Chem., 3163 (1995) and U.S. Patent No. 5,391,766. In addition, various polyene compounds have been disclosed to be useful in the treatment of inflammatory conditions, psoriasis, allergic reactions, and for use in sunscreens in cosmetic preparations. See e.g., U.S. patent Numbers 4,534,979 and 5,320,833. Also, trienediolates of hexadienoic acids have proved useful in the synthesis of retinoic and nor-retinoic acids. See M.J. Aurell, et al., 49 *Tetrahedron,* 6089 (1993). However, to date, compounds that are RXR antagonist (e.g., that bind to RXR and do not activate, but antagonize transcription) and/or RXR selective compounds that have distinct heterodimer selective properties, such that they are capable of manifesting agonist, partial agonist and antagonist properties, have not been identified or characterized.

Summary of the Invention

[0008] The present invention provides novel RXR modulators that selectively bind to RXR receptors in preference to RAR receptors and that, depending upon the receptor and/or cellular context, display activity as full agonists, partial agonists and/or full antagonists on RXR homodimers and/or RXR heterodimers. Thus, these compounds display unique selectivity for RXR heterodimers, and are referred to herein as dimer-selective RXR modulators. The present invention also provides pharmaceutical compositions incorporating these novel compounds and methods for the therapeutic use of such compounds and pharmaceutical compositions.

[0009] These and various other advantages and features of novelty which characterize the invention are pointed out with particularity in the claims annexed hereto and forming a part hereof. However, for a better understanding of the invention, its advantages, and objects obtained by its use, reference should be had to the accompanying drawings and descriptive matter, in which there is illustrated and described preferred embodiments of the invention.

Definitions

[0010] In accordance with the present invention and as used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

[0011] The term alkyl refers a straight-chain, branched-chain, cyclic and combination alkyls, including optional unsaturation (thereby resulting in alkenyls and alkynyls).

[0012] The term heteroalkyl refers to an optionally substituted straight-chain, branched-chain, cyclic and combination C_1 to C_{10} alkyls containing one or more heteroatoms selected from the group consisting of halogen (i.e., F, Cl, Br, I) (including perfluoro alkyls), oxygen, nitrogen and sulfur, including optional unsaturation.

[0013] The term cycloalkyl refers to an optionally substituted C_3 to C_6 group which forms a ring, including optional unsaturation and optional heteroatom (e.g., O, N or S) substitution in or on the cycloalkyl ring.

[0014] The term aryl refers to optionally substituted phenyl, biphenyl, naphthyl or anthracenyl ring systems.

[0015] The term heteroaryl refers to an optionally substituted five-membered or six-membered heterocyclic or other aryl ring containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur, including, without limitation, furyl, pyrrolyl, pyrrolidinyl, thienyl, pyridyl, piperidyl, indolyl, quinolyl, thiazole, benzthiazole and triazole.

[0016] The term arylalkyl or heteroarylalkyl refers to optionally substituted alkyls containing one or more aryl and/or

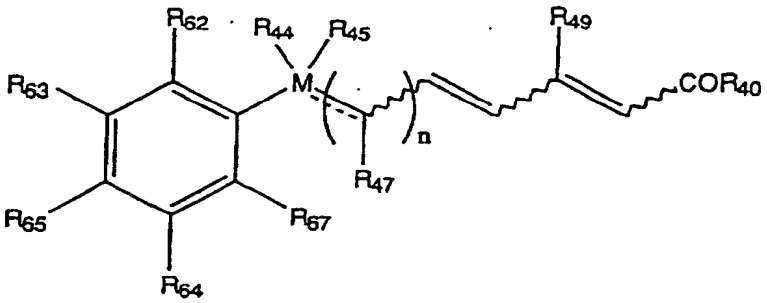
heteroaryl groups.

[0017] The term acyl refers to alkyl, aryl or arylalkyl or heteroarylalkyl substituents attached to a compound via a carbonyl functionality (e.g., -CO-alkyl, -CO-aryl, -CO-arylalkyl or heteroarylalkyl etc...).

[0018] The term dimer-selective RXR modulator refers to a compound that binds to one or more Retinoid X Receptors and modulates (i.e., increases or decreases the transcriptional activity and/or biological properties of the given receptor dimer) the transcriptional activity of an RXR homodimer (i.e., RXR:RXR) and/or RXR in the context of a heterodimer, including but not limited to heterodimer formation with peroxisome proliferator activated receptors (e.g., RXR:PPARα, β,γ1 or γ2), thyroid receptors (e.g., RXR:TRα or β), vitamin D receptors (e.g., RXR:VDR), retinoic acid receptors (e.g., RXR:RARα,β or γ), NGFIB receptors (e.g., RXR:NGFIB), NURR1 receptors (e.g., RXR:NURR1) LXR receptors (e.g., RXR:LXRα,β), DAX receptors (e.g., RXR:DAX), as well as other orphan receptors that form heterodimers with RXR, as either an agonist, partial agonist and/or antagonist. The particular effect of a dimer-selective RXR modulator as an agonist, partial agonist and/or antagonist will depend upon the cellular context as well as the heterodimer partner in which the modulator compounds acts. In this regard, the present invention describes dimer-selective RXR modulators, i.e., modulators that are selective activators and/or repressors through Retinoid X Receptors (i.e., RXRα, RXRβ, and/or RXRγ) rather than Retinoic Acid Receptors (i.e., RARα, RARβ, and/or RARγ).

Detailed Description of Embodiments of the Invention

[0019] In accordance with a first aspect of the present invention, we have developed compounds of the formula:

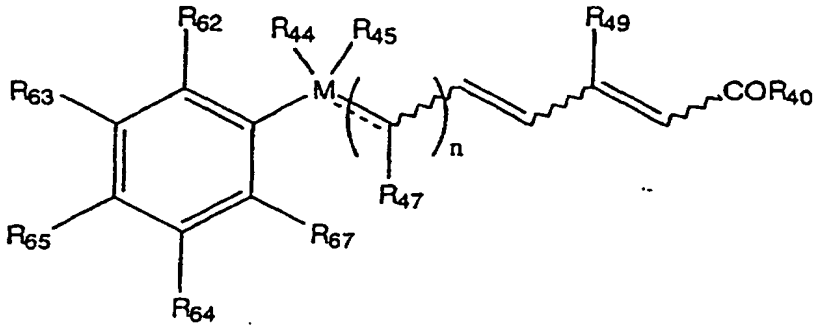


(IV)

wherein, all substituents are as defined in claim 1.

[0020] The compounds of the present invention will find particular application as RXR modulators, and in particular, as dimer-selective RXR modulators, including, but not limited to RXR homodimer antagonists and agonist, partial agonist and antagonists of RXRs in the context of a heterodimer.

[0021] In a second aspect, the present invention provides a use of a dimer-selective RXR modulator compound of the formula:



(IV)

as defined in claim 1 for the preparation of a medicament for modulating processes mediated by RXR homodimers and/or RXR heterodimers by administering to a patient an effective amount of said compound.

[0022] The compounds of the present invention, as well as the compounds utilized in the methods of the present invention, also include all pharmaceutically acceptable salts, as well as esters and amides. As used in this disclosure, pharmaceutically acceptable salts include, but are not limited to: pyridine, ammonium, piperazine, diethylamine, nicotinamide, formic, urea, sodium, potassium, calcium, magnesium, zinc, lithium, cinnamic, methylamino, methanesulfonic, picric, tartaric, triethylamino, dimethylamino, and tris(hydoxymethyl) aminomethane. Additional pharmaceutically acceptable salts are known to those skilled in the art.

[0023] The compounds of the present invention are useful in the modulation of transcriptional activity through an RXR homodimer (i.e., RXR:RXR), as well as through RXR in the context of a heterodimer (e.g., RXR:PPARα,β,γ; RXR:TR; RXR:VDR; RXR:RARα,β,γ; RXR:NGFIB; RXR:NURR1; RXR:LXRα,β, RXR:DAX), including any other intracellular receptors (IRs) which form a heterodimer with RXR. For example, application of the compounds of the present invention to modulate a RXRα:PPARα heterodimer is useful to modulate, i.e. increase HDL cholesterol levels and reduce triglyceride levels. Yet, application of many of the same compounds of the present invention to a RXRα:PPARγ heterodimer modulates a distinct activity, i.e., modulation of adipocyte biology, including effects on the differentiation and apoptosis of adipocytes which will have implications in the treatment and/or prevention of diabetes and obesity. In addition, use of the modulator compounds of the present invention with activators of the other heterodimer partner (e.g., fibrates for PPARα and thiazolidinediones for PPARγ) can lead to a synergistic enhancement of the desired response. Likewise, application of the modulator compounds of the present invention in the contexts of a RXRα:RARα and/or RXRα:VDR heterodimers will be useful to modulate skin related processes (e.g., photoaging, acne, psoriasis), malignant and pre-malignant conditions and programmed cell death (apoptosis). Further, it will be understood by those skilled in the art that the modulator compounds of the present invention will also prove useful in the modulation of other heteromer interactions that include RXR, e.g., trimers, tetramers and the like.

[0024] Thus, the present inventors have discovered novel dimer-selective RXR modulators with multifunctional activity, that selectively bind to RXRs in preference to RARs and that, depending upon the cellular and/or receptor context, can modulate processes as full agonists, partial agonists and/or full antagonists. For example, in the context of an RXR homodimer, the compounds of the present invention function as RXR antagonists, the first demonstration of such RXR antagonism to date. In addition, many of these same compounds show a surprisingly different biology when exerting their effects through an RXR heterodimer. For example, in the context of a RXR:RAR or RXR:PPAR heterodimer, many of the same RXR homodimer antagonist compounds will serve as partial or full agonists, both alone, and in the presence of a corresponding RAR modulator (e.g., all-*trans* retinoic acid (ATRA or TTNPB) or PPAR modulator (e.g., gemfibrizol). In other instances, the compounds of the present invention will also antagonize RXR in the context of a heterodimer.

[0025] Importantly, the dimer-selective RXR modulators of the present invention activate the transcriptional activity of RXRs in the context of heterodimers without the presence of , a corresponding modulator of the other heterodimeric partner (e.g., clofibric acid or gemfibrizol for PPARα; ATRA or TTNPB for RARα). In fact, and in contrast to heterodimers with PPAR, RAR suppresses RXR ligand binding and transactivation for typical RXR agonists (e.g., LGD1069) in the absence of a RAR ligand. However, many of the modulator compounds of the present invention escape suppression by RAR on RXR, and as such, can activate and RAR:RXR heterodimer alone or in the presence of a RAR ligand. While not being bound to a theory of operation, one possible explanation arises from the fact that these unique modulator compounds mechanistically interact with an RXR:RAR heterodimer in a different manner than pure RXR agonists (e.g., LGD1069). Unlike typical RXR agonists, which require an intact activation domain of an RXR receptor in the context of a RAR:RXR heterodimer, the modulator compounds of the present invention require an intact activation domain for the heterodimeric partner (e.g., RAR), but not for the RXR receptor. Accordingly, the modulator compounds of the present invention will, in certain contexts, serve as RAR mimics, activating a subset of the genes activated by typical RAR compounds (e.g., ATRA or TTNPB) and/or activating distinct genes from those activated by typical RAR compounds. In this regard, the modulator compounds of the present invention display many of the benefits of RAR compounds in animals without the typical RAR retinoid-associated toxicities.

[0026] Further, when the modulator compounds of the present invention are combined with a corresponding modulator of the other heterodimeric partner, a surprising synergistic enhancement of the activation of the heterodimer pathway can occur. For example, with respect to a RXRα:PPARα heteodimer, the combination of a compound of the present invention with clofibric acid or gemfibrozil unexpectedly leads to a greater than additive (i.e. synergistic) activation of PPARα responsive genes, which in turn is useful to modulate serum cholesterol and triglyceride levels and other conditions associated with lipid metabolism.

[0027] Whether acting on an RXR heterodimer pathway, or the RXR homodimer pathway. it will also be understood by those skilled in the art that the dimer-selective RXR modulator compounds of the present invention will prove useful in any therapy in which agonists, partial agonists and/or full antagonists of such pathways will find application. Importantly, because the compounds of the present invention can differentially activate RXR homodimers and RXR het-

erodimers, their effects will be tissue and/or cell type specific, depending upon the cellular context of the different tissue types in a given patient. For example, compounds of the present invention will exert an RXR antagonists effect in tissues where RXR homodimers prevail, and partial agonist or full agonist activity on the PPAR pathway where RXRα: PPARα heterodimers prevail (e.g., in liver tissue). Thus, the compounds of the present invention will exert a differential effect in various tissues in an analogous fashion to the manner in which various classes of estrogens and antiestrogens (e.g., Estrogen, Tamoxifen, Raloxifen) exert differential effects in different tissue and/or cell types (e.g., bone, breast, uterus). See e.g., Maty T. Tzukerman et al., 8 Mol. Endo, 21-30 (1994); Donald P. McDonnell et al., 9 Mol. Endo, 659-669 (1995). However, in the present case, it is believed that the differential effects of the compounds of the present invention is based upon the particular dimer pair through which the compound acts, rather than through different trans-activing regions of the estrogen receptor in the case of estrogens and antiestrogens.

[0028] The particular conditions that may be treated with the compounds of the present invention include, skin-related diseases, such as actinic keratoses, arsenic keratoses, inflammatory and non-inflammatory acne, psoriasis, ichthyoses and other keratinization and hyperproliferative disorders of the skin, eczema, atopic dermatitis, Darriers disease, lichen planus, prevention and reversal of glucocorticoid damage (steroid atrophy), as a topical anti-microbial, as skin pigmentation agents and to treat and reverse the effects of age and photo damage to the skin. With respect to the modulation of malignant and pre-malignant conditions, the compounds may also prove useful for the prevention and treatment of cancerous and pre-cancerous conditions, including, premalignant and malignant hyperproliferative diseases and cancers of epithelial origin such as cancers of the breast, skin, prostate, cervix, uterus, colon, bladder, esophagus, stomach, lung, larynx, oral cavity, blood and lymphatic system, metaplasias, dysplasias, neoplasias, leukoplakias and papillomas of the mucous membranes and in the treatment of Kaposis sarcoma. In addition, the present compounds may be used as agents to treat and prevent various cardiovascular diseases, including, without limitation, diseases associated with lipid metabolism such as dyslipidemias, prevention of restenosis and as an agent to increase the level of circulating tissue plasminogen activator (TPA), metabolic diseases such as obesity and diabetes (i.e., non-insulin dependent diabetes mellitus and insulin dependent diabetes mellitus), the modulation of differentiation and proliferation disorders, as well as the prevention and treatment of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Amyotrophic Lateral Sclerosis (ALS), and in the modulation of apoptosis, including both the induction of apoptosis and inhibition of T-Cell activated apoptosis.

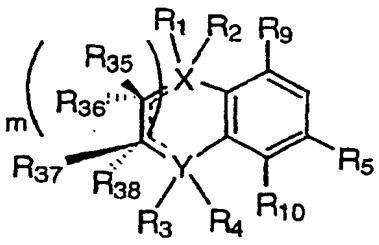
[0029] Furthermore, it will be understood by those skilled in the art that the compounds of the present invention, including pharmaceutical compositions and formulations containing these compounds, can be used in a wide variety of combination therapies to treat the conditions and diseases described above. Thus, the compounds of the present invention can be used in combination with modulators of the other heterodimeric partner with RXR (i.e., in combination with PPARα modulators, such as fibrates, in the treatment of cardiovascular disease, and in combination with PPARγ modulators, such thiazolidinediones, in the treatment of diabetes, including non-insulin dependent diabetes mellitus and insulin dependent diabetes mellitus, and with agents used to treat obesity) and with other therapies, including, without limitation, chemotherapeutic agents such as cytostatic and cytotoxic agents, immunological modifiers such as interferons, interleukins, growth hormones and other cytokines, hormone therapies, surgery and radiation therapy. By utilizing the compounds of the present invention with modulators of the other heterodimeric partner one is able to utilize lower dosages of either or both modulators, thereby leading to a significant decrease is the side-effects associated with such modulators when employed alone at the strengths required to achieve the desired effect. Thus, the modulator compounds of the present invention, when utilized in combination therapies, provide an enhanced therapeutic index (i.e., signficantly enhanced efficacy and/or decrease side-effect profiles) over utilization of the compounds by themselves.

[0030] Representative modulator compounds of the present invention include, without limitation, (2*E*, 4*E*, 6*E*)-7-(3,5-diisopropyl-2-*n*-heptyloxyphenyl)-3-methylocta-2,4,6-trienoic acid (Compound 146); (2*E*, 4*E*, 6*Z*)-7-(3,5-diisopropyl-2-*n*-heptyloxyphenyl)-3-methylocta-2,4,6-trienoic acid (Compound 147); (2*E*, 4*E*,)-7-(3,5-diisopropyl-2-*n*-heptyloxyphenyl)-3-methylocta-2,4-dienoic acid (Compound 148); (2*Z*, 4*E*,)-7-(3,5-diisopropyl-2-*n*-heptyloxyphenyl)-3-methylocta-2,4,dienoic acid (Compound 149); (2*E*, 4*E*, 6*E*)-7-(3,5-diisopropyl-2-benzyloxyphenyl)-3-methylocta-2,4,6-trienoic acid (Compound 150); and (2*E*, 4*E*, 6*E*)-7-(3,5-diisopropyl-2-*n*-butyloxyphenyl)-3-methylocta-2,4,6-trienoic acid (Compound 151).

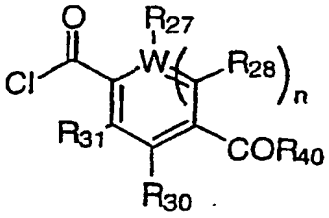
[0031] The compounds of the present invention can be obtained by modification of the compounds disclosed or by a total synthesis approach, by techniques known to those skilled in the art. In this regard, the synthesis of the dimer-specific RXR modulator compounds of the present invention follow established retinoid synthesis schemes and techniques as described in M.I. Dawson and W.H. Okamura, "Chemistry and Biology of Synthetic Retinoids", Chapters 3, 8, 14 and 16, CRC Press, Inc., Florida (1990); M.I. Dawson and P.D. Hobbs, *The Synthetic Chemistry of Retinoids, In* Chapter 2: "The Retinoids, Biology, Chemistry and Medicine", M.B. Sporn et al., Eds. (2nd ed.), Raven Press, New York, New York, pp. 5-178 (1994); R.S.H. Liu and A. E. Asato, "Photochemistry and Synthesis of Stereoisomers of Vitamin A," 40 *Tetrahedron,* 1931 (1984); 43 *Cancer Res.,* 5268 (1983); 15 *Eur. J. Med. Chem.*, 9 (1980); M. Boehm et al., 37 *J. Med. Chem., 2930 (1994)*; M. Boehm et al., 38 *J. Med. Chem.*, 3146 (1995); E. Allegretto et al., 270 *Journal*

of Biol. Chem., 23906 (1995); R. Bissonette et al., 15 *Mol. & Cellular Bio.*, 5576 (1995); R. Beard et al., 38 *J. Med. Chem.*, 2820 (1995), S. Canan Koch et al., 39 *J. Med. Chem.*, 3229 (1996) and U.S. Patent Nos. 4,326,055 and 4,578,498, the disclosures of which are herein incorporated by reference. The sequence of steps of the general schemes of synthesizing the compounds of the present invention are shown below. In addition, more detailed and illustrative synthetic schemes for specific compounds of the present invention will be found in the Examples included herein.

Scheme 1



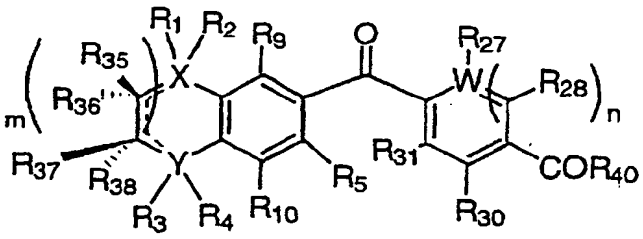
1



2

1. $AlCl_3$
   CH_2Cl_2 / hexanes

2. H_2SO_4 / heat
(3. KOH / H_2O / MeOH)

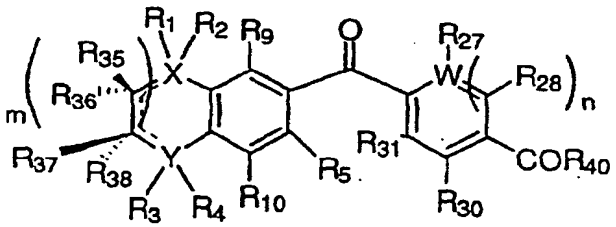


3

NaH / THF

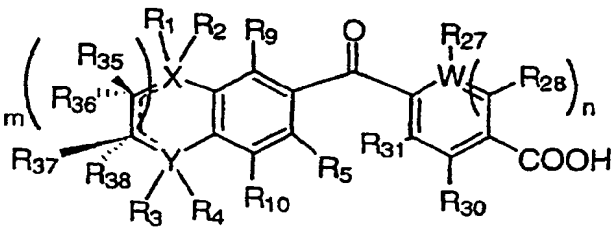
R_8Br

(where R_5 = OH)



4 (R_{40} = OR_{41})

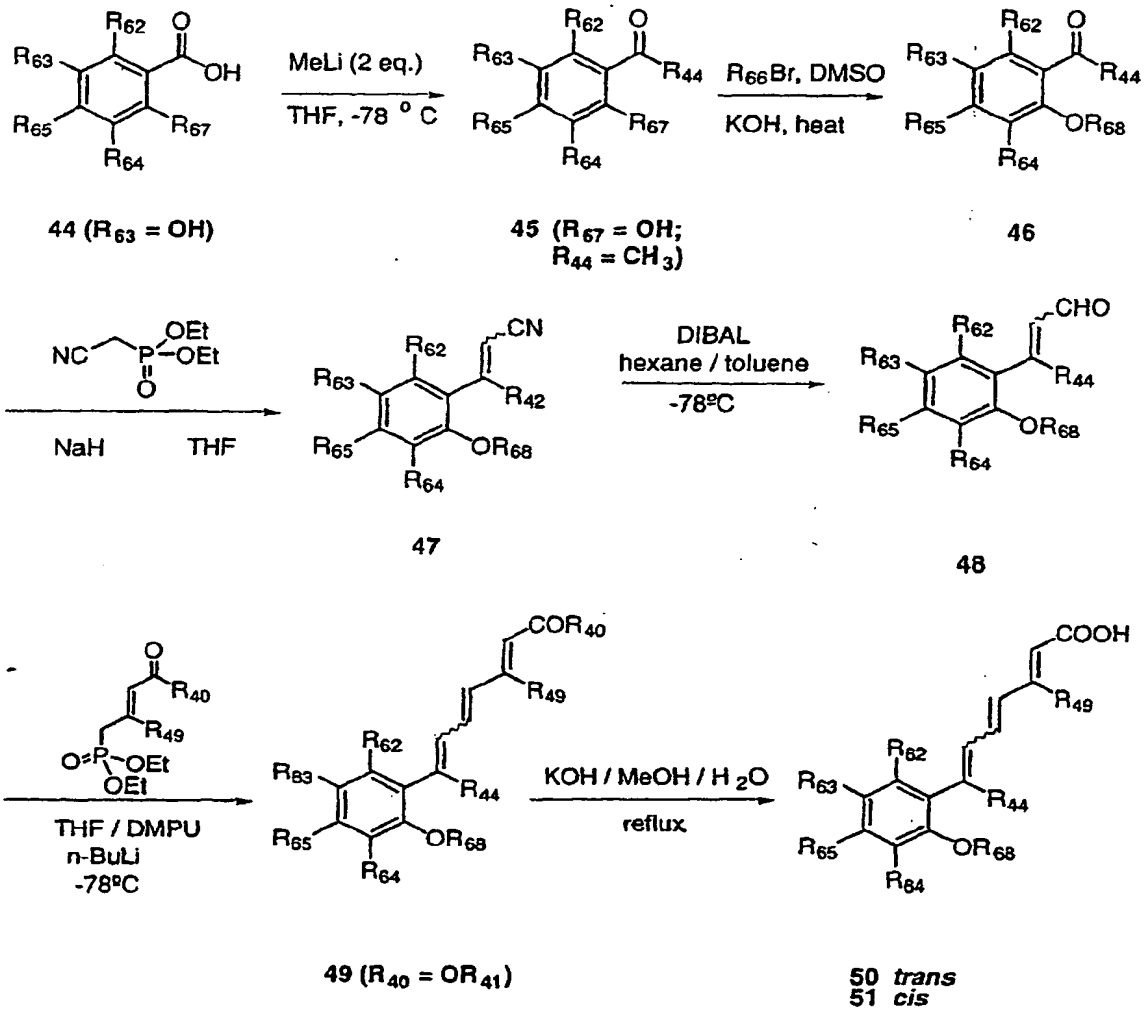
KOH / MeOH



5

[0032] In Scheme 1, the compound 3, a common precursor to the compounds **5 - 12**, may be prepared by Friedel-Crafts acylation of an appropriately substituted tetrahydrotetramethylnaphthalene **1** with an acid chloride **2**, such as monomethyl teraphthalate acid chloride, under Lewis acid (such as aluminum trichloride) and/or protic acid (such as H_2SO_4) catalyzed conditions in solvents such as dichloromethane or dichloroethane. In cases such that the naphthalene has a hydroxy functionality, an *O*-alkylation of the naphthol may be achieved by treatment with a base, such as NaH or K_2CO_3, and an alkyl halide to provide the keto ether **4**. The acid **5** is readily obtainable from the corresponding ester by hydrolysis in an alkanol solvent at ambient temperature with about a three molar excess of base, for example, potassium hydroxide. Alternatively, the ester **4** may be hydrolyzed in THE/water or acetone/water at ambient temperature with, for example, excess lithium hydroxide. The hydrolysis solution is acidified and the hydrolysate recovered by conventional means to provide the keto acid **5**.

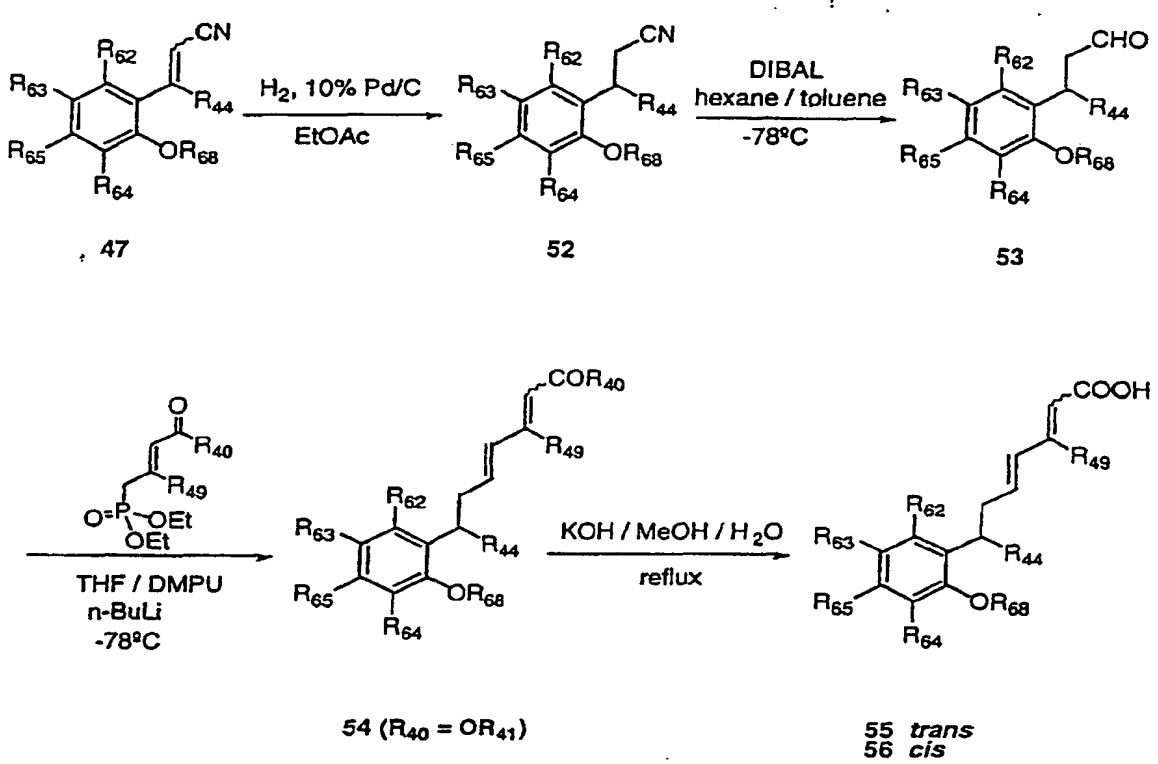
Scheme 15



[0033] The aromatic trienes of the present invention, that is compounds of general structures **50** and **51**, may be prepared in accordance with reaction Scheme 15. The starting materials for this sequence, substituted benzoic acids of general structure **44**, may be treated with alkyl lithiums, such as methyllithium, at low temperatures in solvents such as THF or ether to produce alkyl aryl ketones of general structure **45**. In cases where the aryl group contains a hydroxy functionality, the phenol may be alkylated by treatment with a base, such as KOH, and an alkyl or benzyl halide in a solvent such as DMSO to provide the keto ether **46**. Further, in accordance with this sequence of reactions aryl ketones of general structure **46** are condensed with a phosphonate, such as the sodium or lithium salt of diethyl cyanomethyl-

phosphonate, in THF at ambient or reduced temperatures in a Horner-Wadsworth-Emmons olefination reaction to provide cyano olefin **47**. The cyano olefin **47** is reduced with DIBAL at -78°C to provide the intermediate enal **48**. The solvent to be used in the reduction includes methylene chloride, hexanes, and THF. The *trans* and *cis* isomers may be separated at this stage via thin-layer chromatography (TLC), or other recognized procedures known to those skilled in the art. The aldehyde intermediate is then treated with a phosphonate, such as the lithium salt of diethyl 3-ethoxycarbonyl-2-methylprop-2-enylphosphonate (mixture of double bond isomers) in THF at reduced temperatures in a Horner-Wadsworth-Emmons olefination reaction to provide the trienoate esters **49** where R_{38} is OR_{39}. The olefination reaction is preferably conducted in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU). The acids and salts **50** and **51** are readily obtainable from the corresponding esters by hydrolysis in an alkanol solvent at ambient temperature with about a three molar excess of base, for example, potassium hydroxide. Alternatively, the ethyl esters may be hydrolyzed in THF/water or acetone/water at ambient temperature with, for example, excess lithium hydroxide. The hydrolysis solution is acidified and the hydrolysate recovered by conventional means to give as the major product the (2E, 4E, 6E)-aromatic triene carboxylic acid derivatives of structure **50**. The minor (2E, 4E, 6Z)-aromatic triene geometric isomer, **51**, a by-product of the first olefination reaction, is readily isolated by silica gel chromatography or HPLC purification of the hydrolysate mixture.

Scheme 16



[0034] In accordance with reaction Scheme 16, reduction of the intermediate cyano olefin **47** under an atmosphere of hydrogen gas and in the presence of a catalyst, such as 10% palladium on carbon, provides the saturated nitrile **52**. The nitrile can be reduced in the same fashion as described in reaction Scheme 15 to yield the saturated aldehyde intermediate **53**. The aldehyde **53** is then homologated in the same fashion as described in Scheme 15 to yield as the major product the (2E, 4E)-aromatic diene of general structure **55** and as the minor geometric isomer, the (2Z, 4E)-aromatic diene of general structure **56**.

[0035] It will be understood by those skilled in the art that certain modifications can be made to the above-described methods that remain within the scope of the present invention. For example, the modulator compounds of the present invention may also be produced in the form of the corresponding amides or esters, or pharmaceutically acceptable salts.

[0036] In another aspect, the dimer-selective RXR modulator compounds of the present invention are combined in

a mixture with a pharmaceutically acceptable carrier to provide pharmaceutical compositions useful for treating the biological conditions or disorders noted herein in mammalian, and more preferably, in human patients. The particular carrier employed in these pharmaceutical compositions may take a wide variety of forms depending upon the type of administration desired, e.g., intravenous, oral, topical, suppository, parenteral or in a liposomal formulation.

[0037] In preparing the compositions in oral liquid dosage forms (e.g., suspensions, elixirs and solutions), typical pharmaceutical media, such as water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like can be employed. Similarly, when preparing oral solid dosage forms (e.g., powders, tablets and capsules), carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like will be employed. Due to their ease of administration, tablets and capsules represent the most advantageous oral dosage form for the pharmaceutical compositions of the present invention.

[0038] For parenteral administration, the carrier will typically comprise sterile water, although other ingredients that aid in solubility or serve as preservatives, may also be included. Furthermore, injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like will be employed.

[0039] For topical administration, the compounds of the present invention may be formulated using bland, moisturizing bases, such as ointments or creams. Examples of suitable ointment bases are petrolatum, petrolatum plus volatile silicones, lanolin, and water in oil emulsions such as Eucerin™ (Beiersdorf). Examples of suitable cream bases are Nivea™ Cream (Beiersdorf), cold cream (USP), Purpose Cream™ (Johnson & Johnson), hydrophilic ointment (USP), and Lubriderm™ (Warner-Lambert).

[0040] The pharmaceutical compositions and compounds of the present invention will generally be administered in the form of a dosage unit (e.g., tablet, capsule, etc.) at from about 1 μg/kg of body weight to about 500 mg/kg of body weight, more preferably from about 10 μg/kg to about 250 mg/kg, and most preferably from about 20 μg/kg to about 100 mg/kg. As recognized by those skilled in the art, the particular quantity of pharmaceutical composition according to the present invention administered to a patient will depend upon a number of factors, including, without limitation, the biological activity desired, the condition of the patient, and tolerance for the drug.

[0041] The compounds of this invention also have utility when labeled, either with a radio or stable isotope label, and used in assays to determine the presence of RXRs. They are particularly useful due to their ability to selectively bind to members of the RXR subfamily and can therefore be used to determine the presence of RXR isoforms in the presence of other retinoid receptors or related intracellular receptors.

[0042] Due to the selective specificity of the compounds of this invention for binding to retinoid X receptors, these compounds can also be used to purify samples of RXRs *in vitro*. Such purification can be carried out by mixing samples containing retinoid receptors with one of more of the compounds of the present invention, so that the modulator compound (ligand) binds to the receptor, and then separating out the bound ligand/receptor combination by separation techniques which are known to those of skill in the art. These techniques include column separation, filtration, centrifugation, tagging and physical separation, and antibody complexing, among others.

[0043] The compounds of the present invention also include racemate, individual stereoisomers, including enantiomers and mixtures thereof. These isomers are then isolated by standard resolution techniques, including fractional crystallization and reverse phase and chiral column chromatography.

[0044] The compounds and pharmaceutical compositions of the present invention can advantageously be used in the treatment of the diseases and conditions described herein. In this regard, the dimer-selective modulator compounds and compositions will prove particularly useful in the modulation of processes controlled by RXR homodimers and/or RXR heterodimers, such as apolipoprotein metabolism, either alone, or in combination with PPARs and/or TR modulators such as gemfibrozil or thyroid hormone, as well as modulation of skin-related processes, malignant and pre-malignant conditions and apoptosis, including combinations with RAR and VDR modulators. Likewise, the compounds and compositions will also prove useful in the modulation of processes mediated by RXR homodimers, including selective modulation of programmed cell death (apoptosis). Further, all of these treatment pathways can be triggered without activating the RXR agonist homodimer pathway.

[0045] Furthermore, the modulator compounds and pharmaceutical compositions of the present invention are extremely potent antagonists of a RXR homodimer, typically displaying 50% inhibition of activation of one or more of the retinoid X receptors at a concentration of less than 500 nM, preferably at a concentration of less than 100 nM, more preferably at a concentration of less than 50 nM, more preferably yet at a concentration of less than 20 nM, and most preferably at a concentration of less than 10 nM. Concurrently, the modulator compounds of the present invention are also extremely potent agonists in the context of a RXR heterodimer, typically displaying 50% activation of retinoid X receptors heterodimers at a concentration of less than 500 nM, preferably at a concentration of less than 100 nM, more preferably at a concentration of less than 50 nM, more preferably yet at a concentration of less than 20 nM, and most preferably at a concentration of less than 10 nM. Also, the dimer-selective RXR modulator compounds of the present invention preferentially bind to and inhibit transactivation of one or more of the RXR subfamily of retinoid receptors at a level at least 2 times greater, preferably at least 5 times greater, more preferably at least 10 times greater, and most preferably at least 100 times greater than on the RAR subfamily of retinoid receptors.

[0046] The invention will be further illustrated by reference to the following non-limiting Examples.

Comparative EXAMPLE 1

4-[(3-*n*-Propyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)carbonyl]benzoic acid (Compound 101, prepared as illustrated and described in Scheme 1)

[0047] 3-*n*-Propyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene (prepared from Friedel-Crafts alkylation/cyclization of *n*-propylbenzene with 2,5-dichloro-2,5-dimethyl-hexane) was combined with monomethylterephthalate acid chloride in dichloromethane and treated portionwise at ambient temperature with aluminum chloride until the spontaneous reflux had subsided and the solution became dark red/brown in color. After stirring at room temperature for 10-15 min, the reaction was poured into ice water and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic extracts were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated to give a yellow oil. The crude product was crystallized (CH_2Cl_2 / hexanes) to give 4-[(3-*n*-propyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)carbonyl]benzoic acid methyl ester as white crystals (95%): TLC (20% ethyl acetate: 80% hexanes) R_f 0.7; mp 112-114 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.19 (1/2ABq, J = 8.0 Hz, 2H, ArH); 7.89 (1/2ABq, J = 8.0 Hz, 2H, ArH), 7.22 (s, 1H, ArH), 7.20 (s, 1H, ArH), 3.95 (s, 3H, OCH_3), 2.64 (t, J = 8.0 Hz, 2H, CH_2), 1.69 (s, 4H, $2CH_2$), 1.55 (m, 2H, CH_2), 1.31 (s, 6H, $2CH_3$), 1.20 (s, 6H, $2CH_3$), 0.89 (t, J = 7.5 Hz, 3H, CH_3), Anal. ($C_{23}H_{32}O_3$) C, H. The ester was hydrolyzed in excess KOH/MeOH at ambient temperature for 24 h. The methanol was removed *in vacuo*. The residue was taken-up in water and the aqueous layer was adjusted to pH = 4-5 with 1 M aqueous HCl. The aqueous solution was extracted 3 times with EtOAc; the organic layers were combined, and washed with water (2x) and brine. The organic solution was dried (Na_2SO_4), filtered, and concentrated to give **4-[(3-*n*-propyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)carbonyl]benzoic acid (101).** Crystallization gave a white powder (93%): TLC (10% MeOH: 90%-$CHCl_3$) R_f 0.3; mp 252-254°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.20 (1/2ABq, J = 8.0 Hz, 2H, ArH), 7.90 (1/2ABq, J = 8.0 Hz, 2H, ArH), 7.20 (s, 1H, ArH), 7.25 (s, 1H, ArH), 2.64 (t, J = 8.0 Hz, 2H, CH_2), 1.69 (s, 4H; $2CH_2$), 1.55 (m, 2H, CH_2), 1.31 (s, 6H, $2CH_3$), 1.20 (s, 6H, $2CH_3$), 0.89 (t, J = 7.5 Hz, 3H, CH_3), Anal. ($C_{25}H_{30}O_3$) C, H.

EXAMPLE 46

(2*E*, 4*E*, 6*E*)-7-(3,5-Diisopropyl-2-*n*-heptyloxyphenyl)-3-methylocta-2,4,6-trienoic acid (Compound 146, prepared as illustrated and described in Scheme 15).

[0048] A solution of 3,5-diisopropyl-2-hydroxybenzoic acid (20.0 g, 90.1 mmol) in THF (100 mL) at -78 °C was treated dropwise with a solution of methyllithium (1.4 M in ether, 193 mL, 270 mmol). The reaction solution was allowed to warm to room temperature and stirred for 30 min. The solution was poured into-saturated aqueous NH_4Cl (200 mL), and the organic product was extracted with 1:1 = EtOAc: hexanes (2 X 100 mL), dried ($MgSO_4$), filtered, and concentrated. Distillation (1 mm Hg, 120°C) gave 3,5-diisopropyl-2-hydroxyacetophenone 12.0 g (61%): TLC (5% EtOAc-95% hexanes) R_f=0.4; ^{1}H-NMR ($CDCl_3$) δ 7.39 (s, 1H, ArH),7.29 (s, 1H, ArH), 3.38 (m, 1H, CH), 2.87 (m, 1H, CH), 2.63 (s, 3H, CH_3), 1.24 (d, J = 14.0 Hz, 12H, $4CH_3$).

[0049] A solution of 3,5-diisopropyl-2-hydroxy-acetophenone (1.0 g, 4.54 mmol) DMSO (1 mL) was treated with n-heptylbromide (1 mL, excess) and KOH (solid, 600 mg, 10.7 mmol) at ambient temperature. The mixture was heated at 50° C for 12 h, cooled to room temperature and diluted with water (5 mL) and hexanes (10 mL). The organic layer was separated and washed with water (2 X 5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated to give 3,5-diisopropyl-2-n-heptyloxyacetophenone 1.3 g (90%): ^{1}H-NMR ($CDCl_3$) δ 7.23(s, 1H, ArH), 7.21 (s, 1H, ArH), 3.71(t, J = 7.4 Hz, 2H, OCH_2), 3.32 (m, 1H, CH), 2.87 (m, 1H, CH), 2.63 (s, 3H, CH_3), 1.78 (m, 2H, CH2), 1.31 (m, 8H, $4CH_2$), 1.27 (d, J = 14.0 Hz, 6H, $2CH_3$), 1.24 (d, J = 14.0 Hz, 6H, 2CH3), 0.89 (t, J = 7.5 Hz, 3H, CH3),

[0050] A solution of diethylcyanomethyl phosphonate (2.00 g, 11.18 mmol) in THF (10 mL) at -78° C was treated dropwise with *n*-BuLi (2.5 M in hexanes, 4.4 mL, 11.0 mmol). The reaction solution was allowed to warm to ambient temperature and stirred for 30 min. A solution of the unpurified 3,5-diisopropyl-2-*n*-heptyloxyacetophenone (1.0 g, 3.14 mmol) in THF (5 mL) was added dropwise to the ylide solution. After stirring for 1 h at ambient temperature, the reaction solution was diluted with saturated aqueous NH_4Cl (20 mL) and extracted with hexanes (2 X 20 mL). The organic extracts were combined and washed with water (2 X 5 mL) and brine (5 mL), dried ($MgSO_4$), filtered, and concentrated to give 3-(3,5-diisopropyl-2-*n*-heptyloxyphenyl)-but-2-enenitrile 900 mg (32%), predominantly as the *trans* isomer: TLC (5% EtOAc-95% hexanes) R_f = 0.9; ^{1}H-NMR ($CDCl_3$) δ 7.11(s, 1H, ArH),6.81 (s, 1H, ArH), 5.57 (s, 1H, olefinic), 3.61 (t, J = 7.4 Hz, 2H, OCH_2), 3.32 (m, 1H, CH), 2.84 (m, 1H, CH), 2.46 (s, 3H, CH_3), 1.73 (m, 2H, CH_2), 1.31 (m, 8H, $4CH_2$), 1.27 (d, J = 14.0 Hz, 6H, $2CH_3$), 1.24 (d, J = 14.0 Hz, 6H, $2CH_3$), 0.89 (t, J = 7.5 Hz, 3H, CH_3).

[0051] A solution of 3-(3,5-diisopropyl-2-*n*-heptyloxyphenyl)-but-2-enenitrile (900 mg, 2.64 mmol) in hexanes (8 mL)

was treated with DIBAL (1.5 M in toluene, 2.0 mL, 7.95 mmol) at -78 °C. After stirring for 15 min at -78 °C, the reaction solution was quenched with a saturated aqueous sodium-potassium tartrate solution (20 mL) and allowed to warm to room temperature over 30 min. The product was extracted with ether (2 X 40 mL), and the organic sollution was washed with water (2 X mL) and brine (5 mL), dried ($MgSO_4$), filtered, concentrated. Purification by silica gel flash chromatography (3% EtOAc-hexanes) gave the unsaturated aldehyde 3-(3,5-diisopropyl-2-*n*-heptyloxyphenyl)-but-2-enal 800 mg (90%): TLC (10% EtOAc-90% hexanes) R_f = 0.7; ^{1}H-NMR ($CDCl_3$) δ 10.17 (d, J = 8.0 Hz, 1H, CHO), 7.11(s, 1H, ArH), 6.82 (s, 1H, ArH), 6.17 (d, J = 8 Hz, 1H, olefinic), 3.65 (t, J = 7.4 Hz, 2H, OCH_2), 3.32 (m, 1H, CH), 2.84 (m, 1H, CH), 2.57 (s, 3H, CH_3), 1.73 (m, 2H, CH_2), 1.31 (m, 8H, $4CH_2$), 1.27 (d, J = 14.0 Hz, 6H, $2CH_3$), 1.24 (d, J = 14.0 Hz, 6H, $2CH_3$), 0.89 (t, J = 7.5 Hz, 3H, CH_3).

[0052] A solution of diethyl 3-ethoxycarbonyl-2-methyl prop-2-enylphosphonate (1.0 g, 3.79 mmol) and DMPU (4 mL) in THF (4 mL) was cooled in a -78 °C bath and treated with *n*-BuLi (2.5 M solution in hexanes, 1.5 mL, 3.75 mmol). The reaction solution was allowed to warm to room temperature and stirred for 15 min. A solution of 3-(3,5-diisopropyl-2-*n*-heptyloxyphenyl)-but-2-enal (820 mg, 2.38 mmol) in THF (10 mL) was added and the resulting solution was allowed to stir for 1 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with ether (2 X 20 mL). The combined organic extracts were washed with water (2 X 5 mL) and brine (5 mL), dried ($MgSO_4$), filtered, concentrated and purified by silica gel flash column chromatography (5 % EtOAc-hexanes) to give ethyl-(2*E*, 4*E*, 6*E*)-7-(3,5-diisopropyl-2-*n*-heptyloxyphenyl)-3-methylocta-2,4,6-trienoate 1.0 g (92%): TLC (5% EtOAc-95% hexanes) R_f = 0.8; ^{1}H-NMR ($CDCl_3$) δ 7.01 (s, 1H, ArH), 6.99 (m, 1H, olefinic), 6.84 (s, 1H, Ar), 6.35 (d, J = 11.0 Hz, 1H, olefinic), 6.30 (d, J = 15.0 Hz, 1H, olefinic), 5.79 (s, 1H, olefinic), 4.18 (m, 2H, OCH_2), 3.65 (t, J = 7.4 Hz, 2H, OCH_2), 3.32 (m, 1H, CH), 2.84 (m, 1H, CH), 2.37 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 1.66 (m, 2H, CH_2), 1.31 (m, 8H, $4CH_2$), 1.29 (t, J = 14.0 Hz, 3H, CH_3), 1.27 (d, J = 14.0 Hz, 6H, $2CH_3$), 1.24 (d, J = 14.0 Hz, 6H, $2CH_3$), 0.89 (t, J = 7.5 Hz, 3H, CH_3).

[0053] A solution of the crude ethyl-(2*E*, 4*E*, 6*E*)-7-(3,5-dilsopropyl-2-*n*-heptyloxyphenyl)-3-methylocta-2,4,6-trienoate (500 mg, 1.10 mmol) in methanol (5 mL) was hydrolyzed with NaOH (1 mL of 5N aqueous solution) at reflux temperature. After 10 min, the mixture was cooled to room temperature and acidified with a 20% aqueous HCl solution. The solution was concentrated and the aqueous residue was extracted with EtOAc (2 x 10 mL). The EtOAc layer was washed with water (2 X 5 mL) and brine (5 mL), dried ($MgSO_4$), filtered and concentrated. The major product (highest running spot by TLC) was isolated by preparative TLC (20% EtOAC-80% hexanes) to give **(2*E*, 4*E*, 6*E*)-7-(3,5-diisopropyl-2-*n* heptyloxyphenyl)-3-methylocta-2,4,6-trienoic acid (146)** 220 mg (47%): TLC (10% MeOH-90% $CHCl_3$) R_f = 0.6; ^{1}H-NMR ($CDCl_3$) δ 7.04 (m, 1H, olefinic), 7.01(s, 1H, ArH), 6.84 (s, 1H, ArH), 6.35 (d, J = 11.0 Hz, 1H, olefinic), 6.30 (d, J = 15.0 Hz, 1H, olefinic), 5.79 (s, 1H, olefinic), 3.65 (t, J = 7.4 Hz, 2H, OCH_2), 3.32 (m, 1H, CH), 2.84 (m, 1H, CH), 2.37 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 1.66 (m, 2H, CH_2), 1.31 (m, 8H, $4CH_2$), 1.27 (d, J = 14.0 Hz, 6H, $2CH_3$), 1.24 (d, J = 14.0 Hz, 6H, $2CH_3$), 0.89 (t, J = 7.5 Hz, 3H, CH_3).

EXAMPLE 47

(2*E*, 4*E*, 6*Z*)-7-(3,5-Diisopropyl-2-*n*-heptyloxyphenyl)-3-methylocta-2,4,6-trienoic acid (Compound 147, prepared as illustrated and described in Scheme 15).

[0054] The final product mixture from Example 46 was purified by preparative silica gel thin layer chromatography (20% EtOAc:hexanes) to give the title compound **(2*E*, 4*E*, 6*Z*)-7-(3,5-diisopropyl-2-*n*-heptyloxyphenyl)-3-methylocta-2,4,6-trienoic acid (147)** as a colorless oil: TLC (10% MeOH-90% $CHCl_3$) R_f = 0.6; ^{1}H-NMR ($CDCl_3$) δ 7.26 (d, J = 2.3 Hz, 1H, Ar-H), 7.03 (d, J = 2.3 Hz, 1H, Ar-H), 6.73 (m, 1H, olefinic), 6.24 (d, J = 15.2 Hz, 1H, olefinic), 6.21 (d, J = 10.2 Hz, 1H, olefinic), 5.72 (s, 1H, olefinic), 3.61 (t, J = 6.5 Hz, 2H, OCH_2), 3.34 (m, 1H, CH), 2.85 (m, 1H, CH), 2.21 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 1.64 (m, 2H, CH_2), 1.50 (m, 2H, CH_2), 1.37 (m, 6H, $3CH_3$), 1.27 (d, J = 4.7 Hz, 6H, $2CH_3$), 1.21 (d, J = 4.7 Hz, 6H, $2CH_3$), 0.88 (t, J = 6.5 Hz, 3H, CH_3).

EXAMPLE 48

(2*E*,4*E*,)-7-(3,5-Diisopropyl-2-*n*-heptyloxyphenyl)-3-methylocta-2,4-dienoic acid (Compound 148, prepared as illustrated and described in Scheme 16).

[0055] To a solution of 3-(3,5-di-t-butyl-2-*n*-heptyloxyphenyl)-but-2-enenitrile (900 mg, 2.64 mmol) in EtOAc (5 mL) was added 10% Pd on carbon (20 mg, catalytic amount). The mixture was placed under vacuum for 1 min followed by addition of H_2. After stirring for 24 h under an atmosphere of H_2, the solution was filtered through celite. The celite washed with EtOAc (3 x 5 mL) and the solution was concentrated to give the reduced product 3-(3,5-di-t-butyl-2-*n*-heptyloxyphenyl)butyronitrile 880 mg (97%): TLC (5% EtOAc-95% hexanes) R_f 0.8; ^{1}H-NMR ($CDCl_3$) δ 7.00 (d, J = 2.2 Hz, 1H, Ar-H), 6.89 (d, J = 2.2 Hz, 1H, Ar-H), 3.73 (t, J = 6.5 Hz, 2H, OCH_2), 3.52 (m, 1H, CH), 3.27 (m, 1H, CH),

2.86 (m, 1H, CH), 2.63 (m, 2H, CH_2CN), 1.79 (m, 2H, CH_2), 1.50 (m, 2H, CH_2), 1.44 (m, 6H, $3CH_2$), 1.39 (d, J = 13.2 Hz, 3H, CH_3), 1.27 (d, J = 4.7 Hz, $2CH_3$), 1.21 (d, J = 4.7 Hz, $2CH_3$), 0.89 (t, J = 6.6 Hz, 3H, CH_3).

[0056] To a solution of the (3,5-di-t-butyl-2-*n*-heptyloxyphenyl) butyronitrile (200 mg, 0.58 mmol) in hexanes (5 mL) at -78 °C was added DIBAL (1.5 M solution in toluene, 1.20 mL, 1.80 mmol). The reaction was stirred for 5 min, quenched with saturated aqueous NH_4Cl (10 mL), extracted with ether (2 x 20 mL), dried ($MgSO_4$), filtered, concentrated and purified by chromatography (SiO_2, 5% EtOAc-hexanes) to give the aldehyde 3-(3,5-di-t-butyl-2-*n*-heptyloxyphenyl) butyroacetal 60 mg (30%): TLC (5% EtOAc-95% hexanes) Rf 0.8; ^{1}H-NMR ($CDCl_3$) δ 9.70 (t, J = 2.3 Hz, 1H, CHO), 6.96 (d, J = 2.2 Hz, 1H, Ar-H), 6.86 (d, J = 2.2 Hz, 1H, Ar-H), 3.74 (t, J = 6.5 Hz, 2H, OCH_2), 3.39 (m, 1H, CH), 3.26 (m, 1H, CH), 2.82 (m, 1H, CH), 2.64 (m, 2H, CH2), 1.50 (m, 2H, CH_2), 1.40 (m, 6H, $3CH_2$), 1.32 (d, J = 13.2 Hz, 3H, CH3), 1.27 (d, J = 4.7 Hz, 2CH3), 1.21 (d, J = 4.7 Hz, $2CH_3$), 0.88 (t, J = 6.6 Hz, 3H, CH_3).

[0057] In a manner similar to that described in Example 46, the intermediate aldehyde was converted to ethyl (2*E*, 4*E*)--[7-(3,5-di-t-butyl-2-*n*-heptyloxyphenyl)-3-methyl]-octa-2,4-dienoate: TLC (5% EtOAc-95% hexanes) R_f 0.9; ^{1}H-NMR ($CDCl_3$) δ 6.93 (d, J = 2.2 Hz, 1H, Ar-H), 6.86 (d, J = 2.2 Hz, 1H, Ar-H), 6.06 (m, 2H, 2x olefinic), 5.65 (s, 1H, olefinic), 4.16 (m, 2H, $-CH_2$ CH_3), 3.68 (t, J = 6.5 Hz, 2H, OCH_3), 3.32 (m, 1H, CH), 2.84 (m, 1H, CH), 2.46 (m, 1H, CH), 2.37 (m, 2H, CH_2), 2.22 (s, 3H, CH_3), 1.79 (m, 2H, CH_2), 1.47 (m, 2H, CH2), 1.32 (d, J = 13.2 Hz, 3H, CH_3), 1.31 (m, 6H, $3CH_2$), 1.29 (t, J = 7.0 Hz, 3H, CH3), 1.27 (d, J = 4.7 Hz, 6H, $2CH_3$), 1.21 (d, J = 4.7 Hz, 6H, $2CH_3$), 0.89 (t, J = 7.0 Hz, 3H, CH_3).

[0058] The ester was hydrolyzed as described in Example 46 to give **(2*E*, 4*E*)-7-(3,5-di-t-butyl-2-*n*-heptyloxyphenyl)-3-methylocta-2,4-dienoic acid (148):** TLC (10% MeOH-90% $CHCl_3$) R_f 0.5; ^{1}H-NMR ($CDCl_3$) δ 6.94 (d, J = 2.2 Hz, 1H, Ar-H), 6.86 (d, J = 2.2 Hz, 1H, Ar-H), 6.11 (m, 2H, 2x olefinic), 5.68 (s, 1H, olefinic), 3.68 (t, J = 6.5 Hz, 2H, OCH_3), 3.28 (m, 1H, CH), 2.82 (m, 1H, CH), 2.43 (m, 1H, CH), 2.38 (m, 2H, CH_2), 2.23 (s, 3H, CH3), 1.77 (m, 2H, CH_2), 1.43 (m, 2H, CH_2), 1.34 (m, 6H, $3CH_2$), 1.32 (d, J = 13.2 Hz. 3H, CH_3), 1.27 (t, J = 4.7 Hz, 3H, CH_3), 1.21 (d, J=4.7 Hz, 6H, $2CH_3$), 0.88 (t, J = 6.6 Hz, 3H, CH_3).

EXAMPLE 49

(2*Z*,4*E*,)-7-(3,5-Diisopropyl-2-*n*-heptyloxyphenyl)-3-methylocta-2,4,dienoic acid (Compound 149, prepared as illustrated and described in Scheme 16).

[0059] The final product mixture from Example 48 was purified by preparative silica gel thin layer chromatography (20% EtOAc-hexanes) to give the title compound **(2*Z*, 4*E*,)-7-(3,5-diisopropyl-2-*n*-heptyloxyphenyl)-3-methylocta-2,4,dienoic acid (149)** as a colorless oil: TLC (10% MeOH-90% $CHCl_3$) R_f 0.6; ^{1}H-NMR ($CDCl_3$) δ 7.52 (d, J = 15.8 Hz, 1H, olefinic), 6.93 (d, J = 2.2 Hz, 1H, Ar-H), 6.89 (d, J = 2.2 Hz, 1H, Ar-H), 6.10 (s, 1H, olefinic), 5.60 (s, 1H, olefinic), 3.68 (t, J = 6.5 Hz, 2H, OCH_3), 3.28 (m, 1H, CH), 3.28 (m, 1H, CH), 2.85 (m, 1H, CH), 2.49 (m, 3H, CH-CH_2), 1.97 (s, 3H, CH_3), 1.77 (m, 2H, CH_2), 1.47 (m, 2H, CH_2), 1.31 (m, 6H, $3CH_2$), 1.27 (d, J = 13.2 Hz, 3H, CH_3), 1.24 (t, J = 4.7 Hz, 3H, CH_3), 1.21 (d, J = 4.7 Hz, 6H, $2CH_3$), 0.88 (t, J = 6.6 Hz, 3H, CH_3).

EXAMPLE 50

(2*E*, 4*E*, 6*E*)-7-(3,5-Diisopropyl-2-benzyloxyphenyl)-3-methylocta-2,4,6-trienoic acid (Compound 150, prepared as illustrated and described in Scheme 15).

[0060] The title compound was prepared in an analogous manner as described in Example 46 using 3,5-diisopropyl-2-benzyloxyacetophenone instead of 3,5-diisopropyl-2-*n*-heptyloxyacetophenone to give **(2*E*,4*E*, 6*E*)-7-(3,5-diisopropyl-2-benzyloxyphenyl)-3-methylocta-2,4,6-trienoic acid (150):** TLC (10% MeOH-90% $CHCl_3$) R_f = 0.5; ^{1}H-NMR ($CDCl_3$) δ 7.74 (m, 5H, Ar-H), 7.05 (m, 1H, olefinic), 7.03(s, 1H, ArH), 6.90 (s, 1H, ArH), 6.43 (d, J = 11.0 Hz, 1H, olefinic), 6.34 (d, J = 15.0 Hz, 1H, olefinic), 5.83 (s, 1H, olefinic), 4.71 (s, 2H, OCH_2), 3.39 (m, 1H, CH), 2.88 (m, 1H, CH), 2.40 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 1.26 (m, 12H, $4CH_3$).

EXAMPLE 51

(2*E*, 4*E*, 6*E*)-7-(3,5-Diisopropyl-2-*n*-butyloxyphenyl)-3-methylocta-2,4,6-trienoic acid (Compound 151, prepared as illustrated and described in Scheme 15).

[0061] The title compound was prepared in an analogous manner as described in Example 46 using 3,5-diisopropyl-2-butyloxyacetophenone instead of 3,5-diisopropyl-2-*n*-heptyloxyacetophenone to give **(2*E*, 4*E*, 6*E*)-7-(3,5-diisopropyl-2-*n*-butyloxyphenyl)-3-methylocta-2,4,6-trienoic acid (151):** TLC (10% MeOH-90% $CHCl_3$) R_f= 0.6; ^{1}H-NMR ($CDCl_3$) δ 7.05 (m, 1H, olefinic), 7.03(s, 1H, ArH), 6.85 (s, 1H, ArH), 6.36 (d, J = 11.0 Hz, 1H, olefinic), 6.30 (d, J =

15.0 Hz, 1H, olefinic), 5.83 (s, 1H, olefinic), 3.66 (t, J = 7.4 Hz, 2H, OCH_2), 3.32 (m, 1H, CH), 2.84 (m, 1H, CH), 2.40 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 1.67 (m, 2H, CH2), 1.44 (m, 8H, 4CH2), 1.25 (d, J = 14.0 Hz, 6H, 2CH3), 1.23 (d, J = 14.0 Hz, 6H, 2CH3), 0.92 (t, J = 7.5 Hz, 3H, CH_3).

Evaluation of Retinoid Receptor Subfamily Activity

[0062] Utilizing the "cis-trans" or "co-transfection" assay described by Evans et al., Science, 240:889-95 (May 13, 1988), the disclosure of which is herein incorporated by reference, the dimer-selective RXR modulator compounds of the present invention were tested and found to have strong, specific activity as selective RXR modulators, including activity as full agonists, partial agonists and/or full antagonists of RXR homodimers and/or heterodimers. This assay is described in further detail in U.S. Patent Nos. 4,981,784 and 5,071,773, the disclosures of which are incorporated herein by reference.

[0063] The co-transfection assay provides a method for identifying functional agonists which mimic, or antagonists which inhibit, the effect of native hormones, and quantifying their activity for responsive IR proteins. In this regard, the co-transfection assay mimics an *in vivo* system in the laboratory. Importantly, activity in the co-transfection assay correlates very well with known *in vivo* activity, such that the co-transfection assay functions as a qualitative and quantitative predictor of a tested compounds *in vivo* pharmacology. See, e.g., T. Berger et al. 41 J. Steroid Biochem. Molec. Biol. 773 (1992), the disclosure of which is herein incorporated by reference.

[0064] In the co-transfection assay, cloned cDNA for one or more IRs (e.g., human, murine or rat RXRα, RXRβ, RXRγ, PPARα, VDR, LXR), alone or in combination (i.e. for heterodimer assays) under the control of a constitutive promoter (e.g., the SV 40, RSV or CMV promoter) is introduced by transfection (a procedure to introduce exogenous genes into cells) into a background cell substantially devoid of endogenous IRs. These introduced gene(s) direct the recipient cells to make the IR protein(s) of interest. A further gene is also introduced (co-transfected) into the same cells in conjunction with the IR gene(s). This further gene, comprising the cDNA for a reporter protein, such as firefly luciferase (LUC), controlled by an appropriate hormone responsive promoter containing a hormone response element (HRE). This reporter plasmid functions as a reporter for the transcriptional-modulating activity of the target IR(s). Thus, the reporter acts as a surrogate for the products (mRNA then protein) normally expressed by a gene under control of the target receptor(s) and their native hormone(s).

[0065] The co-transfection assay can detect small molecule agonists or antagonists, including partial agonists and antagonist, of target IRs. Exposing the transfected cells to an agonist ligand compound increases reporter activity in the transfected cells. This activity can-be conveniently measured, e.g., by increasing luciferase production and enzymatic activity, which reflects compound-dependent, IR-mediated increases in reporter transcription. To detect antagonists, the co-transfection assay is carried out in the presence of a constant concentration of an known agonist to the target IR (e.g., 4-[(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl]benzoic acid (LGD1069, Ligand Pharmaceuticals, Inc.) for RXRα) known to induce a defined reporter signal. Increasing concentrations of a suspected antagonist will decrease the reporter signal (e.g., luciferase production). The co-transfection assay is therefore useful to detect both agonists and antagonists of specific IRs. Furthermore, it determines not only whether a compound interacts with a particular IR, but whether this interaction mimics (agonizes) or blocks (antagonizes) the effects of native or synthetic regulatory molecules on target gene expression, as well as the specificity and strength of this interaction.

[0066] The activity of the dimer-selective RXR retinoid modulator compounds of the present invention were evaluated utilizing the co-transfection assay according to the following illustrative Examples.

EXAMPLE 76

RXR Homodimer Co-transfection assay

[0067] CV-1 cells (African green monkey kidney fibroblasts) were cultured in the presence of Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% charcoal resin-stripped fetal bovine serum then transferred to 96-well microtiter plates one day prior to transfection.

[0068] To determine agonist and antagonist activity of the modulator compounds of the present invention, the CV-1 cells or Schneider cells were transiently transfected by calcium phosphate coprecipitation according to the procedure of Berger et al., 41 *J.Steroid Biochem. Mol. Biol.*, 733 (1992) with one or more of the following receptor expressing plasmids: pRShRARα: Giguere *et al.*, 330 Nature, 624 (1987); pRShRARβ and pRShRARγ, Ishikawa *et al.*, 4 Mol. Endocrin., 837 (1990); pRShRXRα, Mangelsdorf *et al.*, 345 Nature, 224 (1990); and pRSmRXRβ and pRSmRXRγ, Mangelsdorf *et al.*, 6 Genes & Devel., 329 (1992), the disclosures of which are herein incorporated by reference. Each of these receptor expressing plasmids was co-transfected at a concentration of 5 ng/well, along with a basal reporter plasmid at 100 ng/well, the internal control plasmid pRS-β-Gal at 50 ng/well and filler DNA , pGEM at 45 ng/well.

[0069] The basal reporter plasmid Δ-MTV-LUC (Hollenberg and Evans, 55 Cell, 899 (1988), the disclosure of which

is herein incorporated by reference) containing an RARE which is referred to as two copies of the TRE-palindromic response element described in Umesono *et al.*, 336 Nature, 262 (1988), the disclosure of which is herein incorporated by reference, was used in transfections for the RARs, and the reporter plasmid CRBPIITKLUC, which contains an RXRE (retinoid X receptor response element, as described in Mangelsdorf *et al.*, 66 Cell, 555 (1991), the disclosure of which is herein incorporated by reference), was used in transfections for the RXRs. Each of these reporter plasmids contains the cDNA for firefly luciferase (LUC) under the control of a promoter containing the appropriate RAR or RXR response element. As noted above, pRS-β-Gal, coding for constitutive expression of E. coli β-galactosidase (β-Gal), was included as an internal control for evaluation of transfection efficiency and compound toxicity.

[0070] Six hours after transfection, media was removed and the cells were washed with phosphate-buffered saline (PBS). Media containing compounds of the present invention in concentrations ranging from 10^{-12} to 10^{-5} M were added to the cells. Similarly, the reference compounds all-*trans* retinoic acid (ATRA)(Sigma Chemical), a known RAR selective agonist compound, and *9-cis* retinoic acid (9-*cis*) (as described in Heyman *et al., Cell,* 68:397-406 (1992)), a compound with known agonist activity on RXRs, were added at similar concentrations to provide a reference point for analysis of the agonist activity of the compounds of the present invention. When determining the antagonist activity of the compounds of the present invention, the compounds were added to the cells in the presence of a fixed concentration (3.2×10^{-8} M) of the known RXR agonist LGD1069 (4-[(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl) ethenyl]benzoic acid: Ligand Pharmaceuticals, Inc.) or the known RAR/RXR panagonist compound (2E,4E,6Z)-7-[5,6,7,8-tetrahydro-5,5,8, 8-tetramethyl-2-naphthalen-2-yl]-3-methyl-octa-2,4,6-trienoic acid (Hoffmann LaRoche, Inc.). Retinoid purity was established as greater than 99% by reverse phase high-performance liquid chromatography. Retinoids were dissolved in dimethylsulfoxide for use in the transcriptional activation assays. Three to four replicates were used for each sample. Transfections and subsequent procedures were performed on a Biomek 1000 automated work station.

[0071] After 40 hours, the cells were washed with PBS, lysed with a Triton X-100-based buffer and assayed for LUC and β-Gal activities using a luminometer or spectrophotometer, respectively. For each replicate, the normalized response (NR) was calculated as:

$$\text{LUC response}/\beta\text{-Gal rate}$$

where β-Gal rate = $\beta\text{-Gal} \bullet 1 \times 10^{-5}/\beta$-Gal incubation time.

[0072] The mean and standard error of the mean (SEM) of the NR were calculated. Data was plotted as the response of the compound compared to the reference compounds over the range of the dose-response curve. For the agonist activity of the compounds of the present invention, the effective concentration that produced 50% of the maximum response (EC_{50}) was quantified. Antagonist activity was determined by testing the amount of LUC expression in the presence of the RAR and/or RXR agonists described above at the EC_{50} concentration for such known compounds. The concentration of compounds of the present invention that inhibited 50% of LUC expression induced by the reference agonist was quantified (IC_{50}). In addition, the efficacy of antagonists was determined as a function (%) maximal inhibition.

RXR and RAR Binding

[0073] In addition to the cotransfection data, the binding of selected compounds of the present invention to the RAR and RXR receptors was also investigated according to the methodology described in M.F., Boehm, et al., "Synthesis and Structure-Activity Relationships of Novel Retinoid X Receptor Selective Retinoids", 37 *J. Med. Chem.,* 2930 (1994); M.F. Boehm, et al., "Synthesis of High Specific Activity [^{3}H]-9-*cis* Retinoic Acid and Its Application for Identifying Retinoids with Unusual Binding Properties", 37 *J. Med. Chem.,* 408 (1994), and E.A. Allegretto, et al., "Characterization and Comparison of Hormone-Binding and Transactivation Properties of Retinoic Acid and Retinoid X Receptors Expressed in Mammalian Cells and Yeast", 268 *J. Biol. Chem.,* 22625 (1993), the disclosures of which are herein incorporated by reference.

[0074] Non-specific binding was defined as that binding remaining in the presence of 500 nM of the appropriate unlabelled compound. At the end of the incubation period, bound from free ligand were separated. The amount of bound tritiated retinoids was determined by liquid scintillation counting of an aliquot (700 μL) of the supernatant fluid or the hydroxylapatite pellet.

[0075] After correcting for non-specific binding, IC_{50} values were determined. The IC_{50} value is defined as the concentration of competing ligand needed to reduce specific binding by 50%. The IC_{50} value was determined graphically from a log-logit plot of the data. The K_d values were determined by application of the Cheng-Prussof equation to the IC_{50} values, the labeled ligand concentration and the K_d of the labeled ligand.

[0076] The IC_{50} antagonist potency (nM) and binding activity (Kd in nM) of selected retinoid modulator compounds

of the present invention on RXRα,β,γ are shown in Table 1 below. In this regard, all of the dimer-selective RXR modulator compounds of the present invention displayed occassionally weak, but most oftetn negligible, if any, agonist activity (i.e., EC_{50}) on all of the RAR and RXR receptors. Accordingly, only RXR antagonist co-transfection data and RXR binding data is provided in Table 1.

Table 1:

Antagonist potency (IC_{50} in nM) in the presence of the known RXR agonist LGD1069, and binding (Kd in nM -v- tritiated LGD1069 and tritiated *9-cis* retinoic acid) of selected dimer-selective RXR modulator compounds of the present invention.

	RXRα	RXRα	RXRβ	RXRβ	RXRγ	RXRγ
Cmpd. No.	**Potency IC_{50} in nM**	**Binding Kd in nM**	**Potency IC_{50} in nM**	**Binding Kd in nM**	**Potency IC_{50} in nM**	**Binding Kd in nM**
146	85	46	29	100	98	116
147	5	3	4	8	8	6
148	89	53	66	87	122	84
149	88	16	129	37	149	42

As can be seen in Table 1, the RXR modulator compounds of the present invention act as antagonists in the context of an RXR:RXR homodimer, with Compound 147 being an especially potent antagonist, both in terms of binding and repression of transactivation of the RXR:RXR homodimer.

EXAMPLE 80

[0077] The following examples provide illustrative pharmacological composition formulations:

[0078] Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/ capsule)
Compound **101**	140
Starch, dried	100
Magnesium stearate	10
Total	250 mg

[0079] The above ingredients are mixed and filled into hard gelatin capsules in 250 mg quantities.

[0080] A tablet is prepared using the ingredients below:

	Quantity (mg/ tablet)
Compound **101**	140
Cellulose, microcrystalline	200
Silicon dioxide, fumed	10
Stearic acid	10
Total	360 mg

[0081] The components are blended and compressed to form tablets each weighing 360 mg. Tablets, each containing 60 mg of active ingredient, are made as follows:

	Quantity (mg/ tablet)
Compound **101**	60
Starch	45

(continued)

	Quantity (mg/ tablet)
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (PVP) (as 10% solution in water)	4
Sodium carboxymethyl starch (SCMS)	4.5
Magnesium stearate	0.5
Talc	1.0
Total	150 mg

[0082] The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of PVP is mixed with the resultant powders, which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The SCMS, magnesium stearate, and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

[0083] Suppositories, each containing 225 mg of active ingredient, may be made as follows:

Compound **101**	225 mg
Saturated fatty acid glycerides	2,000 mg
Total	2,225 mg

[0084] The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of normal 2g capacity and allowed to cool.

[0085] An intravenous formulation may be prepared as follows:

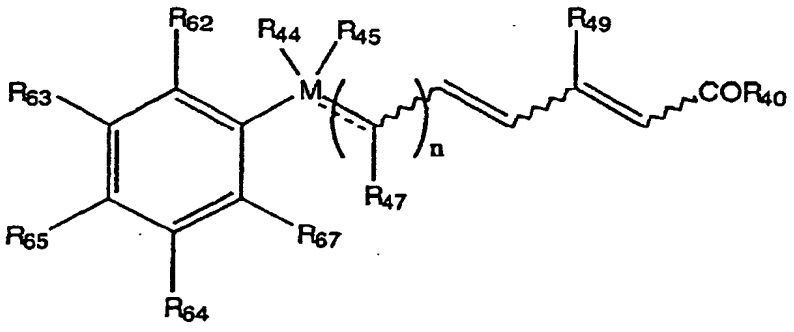
Compound **101**	100 mg
Isotonic saline	1,000 ml
Glycerol	100 ml

[0086] The compound is dissolved in the glycerol and then the solution is slowly diluted with isotonic saline. The solution of the above ingredients is then administered intravenously at a rate of 1 ml per minute to a patient.

[0087] For an understanding of the scope of the present invention, reference is made to the following claims.

Claims

1. A compound of the formula:



(IV)

R_{40} is OR_{41} or $NR_{42}R_{43}$, with R_{41} being hydrogen, a C_1 - C_6 alkyl, alkenyl or alkynyl, or a C_7 - C_{15} arylalkyl, arylalkenyl or arylalkynyl, or heteroarylalkyl, heteroarylalkenyl or heteroarylalkynyl, and with R_{42} and R_{43} each independently being hydrogen, a C_1 - C_6 alkyl, alkenyl or alkynyl, a C_7 - C_{15} arylalkyl, arylalkenyl or arylalkynyl, or heteroarylalkyl, heteroarylalkenyl or heteroarylalkynyl, aryl, ortho-, meta-, or para-substituted hydroxyaryl, or taken together are a C_3 - C_6 cycloalkyl, cycloalkenyl or cycloalkynyl;

R_{44} and R_{45} each independently are hydrogen, a C_1 - C_4 alkyl, alkenyl or alkynyl, or CH_2OR_{46}, where R_{46} is hydrogen or a C_1 - C_6 alkyl, alkenyl or alkynyl, or R_{44} and R_{45} taken together are a C_3 - C_6 cycloalkyl, cycloalkenyl or cycloalkynyl, or cycloheteroalkyl, cycloheteroalkenyl or cycloheteroalkynyl;

R_{47} is hydrogen, a C_1 - C_4 alkyl, alkenyl or alkynyl, or when n=1, R_{47} taken together with R_{44} or R_{45} are a C_3 - C_6 cycloalkyl, cycloalkenyl or cycloalkynyl or cycloheteroalkyl, cycloheteroalkenyl or cycloheteroalkynyl;

R_{49} is C_1 - C_4 alkyl, alkenyl or alkynyl;

R_{62} through R_{64} each independently are hydrogen, aryl, heteroaryl, CF_3, a C_2 - C_6 alkyl, alkenyl or alkynyl, C_2 - C_6 heteroalkyl, heteroalkenyl or heteroalkynyl, or $NR_{51}R_{52}$, where R_{51} and R_{52};

each independently are a C_2 -C_{10} alkyl, alkenyl or alkynyl, heteroalkyl, heteroalkenyl or heteroalkynyl, a C_7 - C_{15} arylalkyl, arylalkenyl or arylalkynyl, or heteroarylalkyl, heteroarylalkenyl or heteroarylalkynyl, a C_3 - C_{10} acyl, provided that only one of R_{51} or R_{52} can be acyl, or R_{51} and R_{52} taken together are C_3 - C_6 cycloalkyl, cycloalkenyl or cycloalkynyl;

R_{65} is hydrogen, a C_1 - C_2 alkyl, alkenyl or alkynyl, or OR_{66}, where R_{66} is a C_1 - C_2 alkyl, alkenyl or alkynyl;

R_{67} is a C_4 - C_{10} alkyl, alkenyl or alkynyl, heteroalkyl, heteroalkenyl or heteroalkynyl, aryl, heteroaryl, a C_7-C_{15} arylalkyl, arylalkenyl or arylalkynyl, or heteroarylalkyl, heteroarylalkenyl or heteroarylalkynyl, $NR_{51}R_{52}$, or OR_{68}, where R_{51} and R_{52} have the definitions described above, and where R_{68} is a C_3 - C_{10} alkyl, alkenyl or alkynyl, heteroalkyl, heteroalkenyl or heteroalkynyl, aryl, heteroaryl, or a C_7 - C_{15} arylalkyl, arylalkenyl or arylalkynyl,or heteroarylalkyl, heteroarylalkenyl or heteroarylalkynyl;

M is N or C;

n is 0 or 1 carbon atoms;

the dashed lines in the structures represent optional double bonds, provided, however, that the double bonds cannot be contiguous, and further provided that when such optional double bonds exist then the substitution patterns around such bonds cannot violate double bond valency; and

the wavy lines represent olefin geometry that is either *cis* (Z) or *trans* (E), and unless otherwise indicated, for substituents R_{40} through R_{68}, all olefin geometric isomers (i.e., *cis* (Z) or *trans* (E)) of the above compounds are included.

2. A compound according to claim 1, wherein the compound is a dimer-selective RXR modulator.

3. A compound according to claim 2, wherein the compound is effective in modulating RXR homodimer interactions.

4. A compound according to claim 3, wherein the compound is a RXR homodimer antagonist.

5. A compound according to claim 2, wherein the compound is effective in modulating RXR heterodimer interactions, and wherein the RXR heterodimer comprises an RXR complexed with another intracellular receptor that forms a heterodimer with RXR.

6. A compound according to claim 5, wherein the compound is a RXR heterodimer antagonist.

7. A compound according to claim 5, wherein the RXR is selected from the group consisting of RXRα, RXRβ and RXRγ.

8. A compound according to claim 5, wherein the other intracelluar receptor is selected from the group consisting of PPARα, PPARβ, PPARγ1, PPARγ2, TRα, TRβ, VDRs, RARα, RARβ, RARγ, NGFIBs, NURR1s, LXRα, LXRβ and DAXs.

9. A compound according to claim 2, wherein the compound is effective in treating skin-related diseases and conditions, cancerous and pre-cancerous conditions, diseases of the eye, cardiovascular diseases, metabolic diseases, obesity, inflammatory diseases, neurodegenerative diseases, diseases involving modulation of apoptosis, diseases involving modulation of cellular proliferation, diseases involving modulation of cellular differentiation, diseases of the immune system, improper pituitary function, diseases involving human papilloma virus, wound healing or restoration of hair growth.

10. A compound according to claim 9, wherein the compound is effective in treating non-insulin dependent diabetes mellitus and insulin dependent diabetes mellitus.

11. A compound according to claim 2 selected from the group consisting of (2*E*, 4*E*, 6*E*)-7-(3,5-diisopropyl-2-*n*-heptyloxyphenyl)-3-methylocta-2,4,6-trienoic acid (Compound 146); (2*E*, 4*E*, 6*Z*)-7-(3,5-diisopropyl-2-*n*-heptyloxyphenyl)-3-methylocta-2,4,6-trienoic acid (Compound 147); (2*E*, 4*E*,)-7-(3,5-diisopropyl-2-n-heptyloxyphenyl)-3-methylocta-2,4-dienoic acid (Compound 148); (2*Z*, 4*E*,)-7-(3,5-diisopropyl-2-*n*-heptyloxyphenyl)-3-methylocta-2,4,dienoic acid (Compound 149); (2*E*, 4*E*, 6*E*)-7-(3,5-diisopropyl-2-benzyloxyphenyl)-3-methylocta-2,4,6-trienoic acid (Compound 150); (2*E*, 4*E*, 6*E*)-7-(3,5-diisopropyl-2-*n*-butyloxyphenyl)-3-methylocta-2,4,6-trienoic acid (Compound 151).

12. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound according to claim 2 and a pharmaceutically acceptable carrier.

13. A pharmaceutical composition according to claim 12, wherein the composition is formulated for oral, topical, intravenous, suppository or parental administration.

14. A pharmaceutical composition according to claim 13, wherein the composition is effective to treat skin-related diseases and conditions, cancerous and pre-cancerous conditions, diseases of the eye, cardiovascular diseases, metabolic diseases, obesity, inflammatory diseases, neurodegenerative diseases, diseases involving modulation of apoptosis, diseases involving modulation of cellular proliferation, diseases involving modulation of cellular differentiation, diseases of the immune system, improper pituitary function, diseases involving human papilloma virus, wound healing or restoration of hair growth.

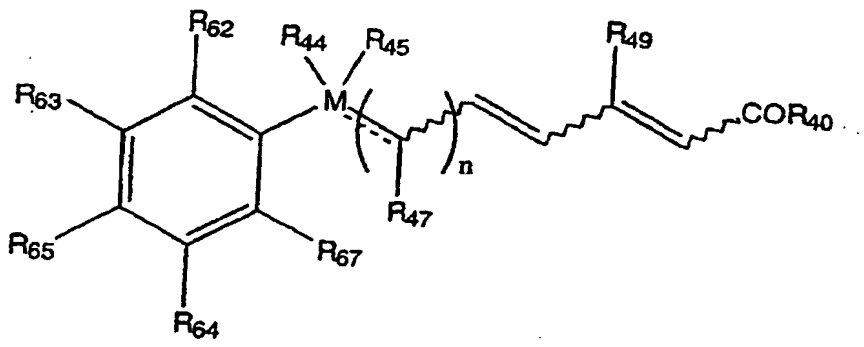
15. A compound according to claim 14, wherein the compound is effective in treating non-insulin dependent diabetes mellitus and insulin dependent diabetes mellitus.

16. A pharmaceutical composition according to claim 12, wherein the composition is administered to a patient as a dosage unit at from about 1μg/kg of body weight to about 500 mg/kg of body weight.

17. A pharmaceutical composition according to claim 12, wherein the composition is administered to a patient as a dosage unit at from about 10μg/kg of body weight to about 250 mg/kg of body weight.

18. A pharmaceutical composition according to claim 12, wherein the composition is administered to a patient as a dosage unit at from about 20μg/kg of body weight to about 100 mg/kg of body weight.

19. Use of a dimer-selective RXR modulator compound of the formula:



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as defined in claim 1;

for the preparation of a medicament for modulating processes mediated by RXR homodimers and/or RXR heterodimers by administering to a patient an effective amount of said compound.

20. Use according to claim 19, wherein the process is mediated by RXR homodimers.

21. Use according to claim 19, wherein the process is mediated by RXR heterodimers.

22. Use according to claim 19, wherein the process is selected from the group consisting of skin-related diseases and conditions, cancerous and pre-cancerous conditions, diseases of the eye, cardiovascular diseases, metabolic diseases, obesity, inflammatory diseases, neurodegenerative diseases, diseases involving modulation of apoptosis, modulation of diseases involving cellular proliferation, modulation of diseases involving cellular differentiation, diseases of the immune system, improper pituitary function, diseases involving human papilloma virus, wound healing and restoration of hair growth.

23. Use according to claim 22, wherein the metabolic disease process is selected from the group consisting of non-insulin dependent diabetes mellitus and insulin dependent diabetes mellitus.

24. Use according to claim 19, wherein the dimer-selective RXR modulator compound is combined with a pharmaceutically acceptable carrier to form a pharmaceutical composition.

25. Use according to claim 24, wherein the pharmaceutical composition is formulated for oral, topical, intravenous, suppository or parental administration.

26. Use according to claim 24, wherein the pharmaceutical composition is effective to treat processes selected from the group consisting of skin-related diseases and conditions, cancerous and pre-cancerous conditions, diseases of the eye, cardiovascular diseases, metabolic diseases, obesity, inflammatory diseases, neurodegenerative diseases, diseases involving modulation of apoptosis, diseases involving modulation of cellular proliferation, diseases involving modulation of cellular differentiation, diseases of the immune system, improper pituitary function, diseases involving human papilloma virus, wound healing and restoration of hair growth.

27. Use according to claim 26, wherein the metabolic disease process is selected from the group consisting of non-insulin dependent diabetes mellitus and insulin dependent diabetes mellitus.

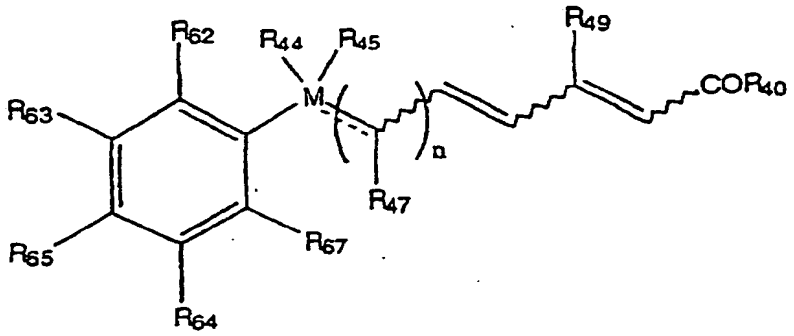
28. Use according to claim 24, wherein the composition is administered to a patient as a dosage unit at from about 1μg/kg of body weight to about 500 mg/kg of body weight.

29. Use according to claim 24, wherein the composition is administered to a patient as a dosage unit at from about 10μg/kg of body weight to about 250 mg/kg of body weight.

30. Use according to claim 24, wherein the composition is administered to a patient as a dosage unit at from about 20μg/kg of body weight to about 100 mg/kg of body weight.

Patentansprüche

1. Verbindung der Formel:



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wobei
R_{40} gleich OR_{41} oder $NR_{42}R_{43}$ ist, wobei R_{41} gleich Wasserstoff, ein C_1-C_6-Alkyl, Alkenyl oder Alkinyl oder ein C_7-C_{15}-Arylalkyl, Arylalkenyl oder Arylalkinyl oder Heteroarylalkyl, Heteroarylalkenyl oder Heteroarylalkinyl ist und wobei R_{42} und R_{43} jeweils unabhängig Wasserstoff, ein C_1-C_6-Alkyl, Alkenyl oder Alkinyl, ein C_7-C_{15}-Arylalkyl, Arylalkenyl oder Arylalkinyl oder Heteroarylalkyl, Heteroarylalkenyl oder Heteroarylalkinyl, Aryl, ortho-, meta- oder para-substituiertes Hydroxyaryl sind oder zusammen ein C_3-C_6-Cycloalkyl, Cycloalkenyl oder Cycloalkinyl darstellen;
R_{44} und R_{45} jeweils unabhängig Wasserstoff, ein C_1-C_4-Alkyl, Alkenyl oder Alkinyl oder CH_2OR_{46} sind, wobei R_{46} gleich Wasserstoff oder ein C_1-C_6-Alkyl, Alkenyl oder Alkinyl ist, oder R_{44} und R_{45} zusammen ein C_3-C_6-Cycloalkyl, Cycloalkenyl oder Cycloalkinyl oder Cycloheteroalkyl, Cycloheteroalkenyl oder Cycloheteroalkinyl darstellen;
R_{47} gleich Wasserstoff, ein C_1-C_4-Alkyl, Alkenyl oder Alkinyl ist, oder wenn n = 1, R_{47} zusammen mit R_{44} oder R_{45} ein C_3-C_6-Cycloalkyl, Cycloalkenyl oder Cycloalkinyl oder Cycloheteroalkyl, Cycloheteroalkenyl oder Cycloheteroalkinyl darstellen;
R_{49} gleich C_1-C_4-Alkyl, Alkenyl oder Alkinyl ist;
R_{62} bis R_{64} jeweils unabhängig Wasserstoff, Aryl, Heteroaryl, CF_3, ein C_2-C_6-Alkyl, Alkenyl oder Alkinyl, C_2-C_6-Heteroalkyl, Heteroalkenyl oder Heteroalkinyl oder $NR_{51}R_{52}$ sind, wobei R_{51} and R_{52} jeweils unabhängig ein C_2-C_{10}-Alkyl, Alkenyl oder Alkinyl, Heteroalkyl, Heteroalkenyl oder Heteroalkinyl, ein C_7-C_{15}-Arylalkyl, Arylalkenyl oder Arylalkinyl oder Heteroarylalkyl, Heteroarylalkenyl oder Heteroarylalkinyl, ein C_3-C_{10}-Acyl sind, unter der Vorraussetzung, daß lediglich einer von R_{51} oder R_{52} gleich Acyl sein kann oder R_{51} und R_{52} zusammen ein C_3-C_6-Cycloalkyl, Cycloalkenyl oder Cycloalkinyl darstellen;
R_{65} gleich Wasserstoff, ein C_1-C_2-Alkyl, Alkenyl oder Alkinyl oder OR_{66} ist, wobei R_{66} ein C_1-C_2-Alkyl, Alkenyl oder Alkinyl ist;
R_{67} ein C_4-C_{10}-Alkyl, Alkenyl oder Alkinyl, Heteroalkyl, Heteroalkenyl oder Heteroalkinyl, Aryl, Heteroaryl, ein C_7-C_{15}-Arylalkyl, Arylalkenyl oder Arylalkinyl oder Heteroarylalkyl, Heteroarylalkenyl oder Heteroarylalkinyl, $NR_{51}R_{52}$ oder OR_{68} ist, wobei R_{51} und R_{52} die oben beschriebenen Bedeutungen besitzen und wobei R_{68} ein C_3-C_{10}-Alkyl, Alkenyl oder Alkinyl, Heteroalkyl, Heteroalkenyl oder Heteroalkinyl, Aryl, Heteroaryl oder ein C_7-C_{15}-Arylalkyl, Arylalkenyl oder Arylalkinyl oder Heteroarylalkyl, Heteroarylalkenyl oder Heteroarylalkinyl ist;
M gleich N oder C ist;
n gleich 0 oder 1 Kohlenstoffatom ist;
die gestrichelten Linien in der Struktur optionale Doppelbindungen darstellen, jedoch unter der Vorraussetzung, daß die Doppelbindungen nicht benachbart sein können, und daß ferner, wenn solche optionalen Doppelbindung existieren, die Substitutionsmuster um solche Bindungen herum dann die Doppelbindungsvalenz nicht verletzen können; und
die wellenförmigen Linien eine Olefingeometrie darstellen, die entweder cis (Z) oder trans (E) ist, und, sofern nicht anders angegeben, für die Substituenten R_{40} bis R_{68} alle Olefingeometrieisomere (d.h. cis (Z) oder trans (E)) der obigen Verbindungen umfaßt sind.

2. Verbindung nach Anspruch 1, wobei die Verbindung ein dimerselektiver RXR-Modulator ist.

3. Verbindung nach Anspruch 2, wobei die Verbindung wirksam bei der Modulation von RXR-Homodimer-Wechselwirkungen ist.

4. Verbindung nach Anspruch 3, wobei die Verbindung ein RXR-Homodimerantagonist ist.

5. Verbindung nach Anspruch 2, wobei die Verbindung wirksam bei der Modulation von RXR-Homodimer-Wechselwirkungen ist und wobei das RXR-Heterodimer einen RXR umfaßt, der mit einem anderen intrazellulären Rezeptor, der mit RXR ein Heterodimer bildet, komplexiert ist.

6. Verbindung nach Anspruch 5, wobei die Verbindung ein RXR-Heterodimerantagonist ist.

7. Verbindung nach Anspruch 5, wobei der RXR aus der aus RXRα, RXRβ und RXRγ bestehenden Gruppe ausgewählt ist.

8. Verbindung nach Anspruch 5, wobei der andere intrazelluläre Rezeptor aus der Gruppe ausgewählt ist, bestehend aus PPARα, PPARβ, PPARγ1, PPARγ2, TRα, TRβ, VDRs, RARα, RARβ, RARγ, NGFIBs, NURR1s, LXRα, LXRβ und DAXs.

9. Verbindung nach Anspruch 2, wobei die Verbindung wirksam ist bei der Behandlung von Hauterkrankungen und -zuständen, kanzerösen und präkanzerösen Zuständen, Erkrankungen des Auges, Herzkreislauferkrankungen, Stoffwechselerkrankungen, Fettleibigkeit, entzündlichen Erkrankungen, neurodegenerativen Erkrankungen, Erkrankungen, die mit einer Modulation der Apoptose zu tun haben, Erkrankungen, die mit einer Modulation der Zellproliferation zu tun haben, Erkrankungen, die mit einer Modulation der Zelldifferentiation zu tun haben, Erkrankungen des Immunsystems, unzureichender Hirnanhangdrüsenfunktion, Erkrankungen im Zusammenhang mit dem Human Papilloma Virus, der Wundheilung oder Wiederherstellung des Haarwachstums.

10. Verbindung nach Anspruch 9, wobei die Verbindung wirksam ist bei der Behandlung der nicht insulinabhängigen Diabetes mellitus und der insulinabhängigen Diabetes mellitus.

11. Verbindung nach Anspruch 2, welche aus der Gruppe ausgewählt ist, bestehend aus (2E, 4E, 6E)-7-(3,5-Diisopropyl-2-n-heptyloxyphenyl)-3-methylocta-2,4,6-triensäure (Verbindung 146); (2E, 4E, 6Z)-7-(3,5-Diisopropyl-2-n-heptyloxyphenyl)-3-methylocta-2,4,6-triensäure (Verbindung 147); (2E, 4E,)-7-(3,5-Ddiisopropyl-2-n-heptyloxyphenyl)-3-methylocta-2,4-diensäure (Verbindung 148); (2Z, 4E,)-7-(3,5-Diisopropyl-2-n-heptyloxyphenyl)-3-methylocta-2,4-diensäure (Verbindung 149); (2E, 4E, 6E)-7-(3,5-Diisopropyl-2-benzyloxyphenyl)-3-methylocta-2,4,6-triensäure (Verbindung 150); (2E, 4E, 6E)-7-(3,5-Diisopropyl-2-nbutyloxyphenyl)-3-methylocta-2,4,6-triensäure (Verbindung 151).

12. Pharmazeutische Zusammensetzung, die eine pharmazeutisch wirksame Menge einer Verbindung gemäß Anspruch 2 und einen pharmazeutisch akzeptablen Träger umfaßt.

13. Pharmazeutische Zusammensetzung nach Anspruch 12, wobei die Zusammensetzung für eine orale, örtliche, intravenöse, suppositorische oder parenterale Verabreichung formuliert ist.

14. Pharmazeutische Zusammensetzung nach Anspruch 13, wobei die Zusammensetzung wirksam ist bei der Behandlung von Hauterkrankungen und -zuständen, kanzerösen und präkanzerösen Zuständen, Erkrankungen des Auges, Herzkreislauferkrankungen, Stoffwechselerkrankungen, Fettleibigkeit, entzündlichen Erkrankungen, neurodegenerativen Erkrankungen, Erkrankungen, die mit einer Modulation der Apoptose zu tun haben, Erkrankungen, die mit einer Modulation der Zellproliferation zu tun haben, Erkrankungen, die mit einer Modulation der Zelldifferentiation zu tun haben, Erkrankungen des Immunsystems, unzureichender Hirnanhangdrüsenfunktion, Erkrankungen im Zusammenhang mit dem Human Papilloma Virus, der Wundheilung oder Wiederherstellung des Haarwachstums.

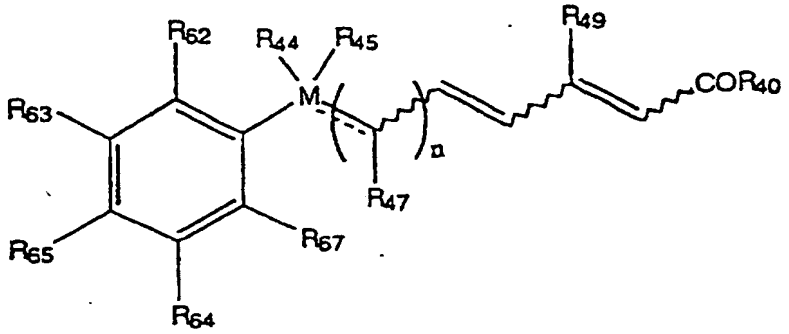
15. Verbindung nach Anspruch 14, wobei die Verbindung wirksam ist bei der Behandlung der nicht insulinabhängigen Diabetes mellitus und der insulinabhängigen Diabetes mellitus.

16. Pharmazeutische Zusammensetzung nach Anspruch 12, wobei die Zusammensetzung einem Patienten mit einer Dosiseinheit von ungefähr 1 µg/kg an Körpergewicht bis ungefähr 500 mg/kg an Körpergewicht verabreicht wird.

17. Pharmazeutische Zusammensetzung nach Anspruch 12, wobei die Zusammensetzung einem Patienten mit einer Dosiseinheit von ungefähr 10 µg/kg an Körpergewicht bis ungefähr 250 mg/kg an Körpergewicht verabreicht wird.

18. Pharmazeutische Zusammensetzung nach Anspruch 12, wobei die Zusammensetzung einem Patienten mit einer Dosiseinheit von ungefähr 20 µg/kg an Körpergewicht bis ungefähr 100 mg/kg an Körpergewicht verabreicht wird.

19. Verwendung einer dimerselektiven RXR-Modulatorverbindung der wie in Anspruch 1 definierten Formel:



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zur Herstellung eines Medikaments zur Modulation von Prozessen, die durch RXR-Homodimere und/oder RXR-Heterodimere mediiert werden, indem dem Patienten eine wirksamen Menge der Verbindung verabreicht wird.

20. Verwendung nach Anspruch 19, wobei der Prozeß durch RXR-Homodimere mediiert wird.

21. Verwendung nach Anspruch 19, wobei der Prozeß durch RXR-Heterodimere mediiert wird.

22. Verwendung nach Anspruch 19, wobei der Prozeß ausgewählt ist aus der Gruppe, bestehend aus Hauterkrankungen und -zuständen, kanzerösen und präkanzerösen Zuständen, Erkrankungen des Auges, Herzkreislauferkrankungen, Stoffwechselerkrankungen, Fettleibigkeit, entzündlichen Erkrankungen, neurodegenerativen Erkrankungen, Erkrankungen, die mit einer Modulation der Apoptose zu tun haben, einer Modulation von Erkrankungen, die mit der Zellproliferation zu tun haben, einer Modulation von Erkrankungen, die mit der Zelldifferentiation zu tun haben, Erkrankungen des Immunsystems, unzureichender Hirnanhangdrüsenfunktion, Erkrankungen im Zusammenhang mit dem Human Papilloma Virus, Wundheilung und Wiederherstellung des Haarwachstums.

23. Verwendung nach Anspruch 22, wobei der Stoffwechselerkrankungsprozeß ausgewählt ist aus der Gruppe, bestehend aus nicht insulinabhängiger Diabetes mellitus und insulinabhängiger Diabetes mellitus.

24. Verwendung nach Anspruch 19, wobei die dimerselektive RXR-Modulatorverbindung mit einem pharmazeutisch akzeptablen Träger kombiniert wird, um eine pharmazeutische Zusammensetzung zu bilden.

25. Verwendung nach Anspruch 24, wobei die pharmazeutische Zusammensetzung für eine orale, örtliche, intravenöse, suppositorische oder parenterale Verabreichung formuliert ist.

26. Verwendung nach Anspruch 24, wobei die pharmazeutische Zusammensetzung wirksam ist bei der Behandlung von Prozessen, die aus der Gruppe ausgewählt sind, bestehend aus Hauterkrankungen und -zuständen, kanzerösen und präkanzerösen Zuständen, Erkrankungen des Auges, Herzkreislauferkrankungen, Stoffwechselerkrankungen, Fettleibigkeit, entzündlichen Erkrankungen, neurodegenerativen Erkrankungen, Erkrankungen, die mit einer Modulation der Apoptose zu tun haben, Erkrankungen, die mit einer Modulation der Zellproliferation zu tun haben, Erkrankungen, die mit einer Modulation der Zelldifferentiation zu tun haben, Erkrankungen des Immunsystems, unzureichender Hirnanhangdrüsenfunktion, Erkrankungen im Zusammenhang mit dem Human Papilloma Virus, Wundheilung und Wiederherstellung des Haarwachstums.

27. Verwendung nach Anspruch 26, wobei der Stoffwechselerkrankungsprozeß ausgewählt ist aus der Gruppe, bestehend aus nicht insulinabhängiger Diabetes mellitus und insulinabhängiger Diabetes mellitus.

28. Verwendung nach Anspruch 24, wobei die Zusammensetzung einem Patienten mit einer Dosiseinheit von ungefähr 1 µg/kg an Körpergewicht bis ungefähr 500 mg/kg an Körpergewicht verabreicht wird.

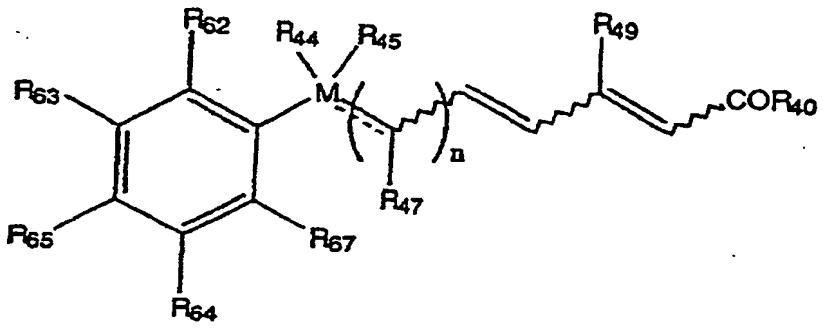
29. Verwendung nach Anspruch 24, wobei die Zusammensetzung einem Patienten mit einer Dosiseinheit von ungefähr

10 µg/kg an Körpergewicht bis ungefähr 250 mg/kg an Körpergewicht verabreicht wird.

30. Verwendung nach Anspruch 24, wobei die Zusammensetzung einem Patienten mit einer Dosiseinheit von ungefähr 20 µg/kg an Körpergewicht bis ungefähr 100 mg/kg an Körpergewicht verabreicht wird.

Revendications

1. Composé de la formule :



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dans laquelle :

R_{40} est OR_{41} ou $NR_{42}R_{43}$, avec R_{41} étant l'hydrogène, un alcényle, alcynyle ou alkyle en C_1-C_6, ou un arylalcényle, arylalcynyle ou arylalkyle en C_7-C_{15}, ou un hétéroarylalkyle, hétéroarylalcényle ou hétéroarylalcynyle et avec R_{42} et R_{43} étant chacun indépendamment hydrogène, un alkyle, alcényle ou alcynyle en C_1-C_6, un arylalkyle, arylalcényle ou arylalcynyle en C_7-C_{15}, ou hétéroarylalkyle, hétéroarylalcényle ou hétéroarylalcynyle, aryle, hydroxyaryl substitué en ortho-, méta- ou para- ou pris conjointement, sont cycloalkyle, cycloalcényle ou cycloalcynyle en C_3-C_6;

R_{44} et R_{45} sont chacun indépendamment l'hydrogène, un alkyle, alcényle ou alcynyle en C_1-C_4, ou CH_2OR_{46}, où R_{46} est l'hydrogène ou un alkyle, alcényle ou alcynyle en C_1-C_6, ou R_{44} et R_{45} pris conjointement sont un cycloalkyle, cycloalcényle ou cycloalcynyle en C_3-C_6, ou cyclohétéroalkyle, cyclohétéroalcényle ou cyclohétéroalcynyle ;

R_{47} est l'hydrogène, un alkyle, alcényle ou alcynyle en C_1-C_4, ou lorsque n = 1, R_{47} pris conjointement avec R_{44} ou R_{45} sont cycloalkyle, cycloalcényle ou cycloalcynyle en C_3-C_6 ou cyclohétéroalkyle, cyclohétéroalcényle ou cyclohétéroalcynyle ;

R_{49} est alkyle, alcényle ou alcynyle en C_1-C_4;

chacun indépendamment sont un alkyle, alcényle ou alcynyle en C_2-C_{10}, hétéroalkyle, hétéroalcényle ou hétéroalcynyle, un arylalkyle, arylalcényle ou arylalcynyle en C_7-C_{15} ou hétéroarylalkyle, hétéroarylalcényle ou hétéroarylalcynyle, un acyle en C_3-C_{10}, dans la mesure où seul un de R_{51} ou R_{52} peut être acyle ou R_{51} et R_{52} pris conjointement sont cycloalkyle, cycloalcényle ou cycloalcynyle en C_3-C_6;

R_{62} à R_{64} sont indépendamment l'hydrogène, aryle, hétéroaryle, CF_3, un alkyle, alcényle ou alcynyle en C_2-C_6, hétéroalkyle, hétéroalcényle ou hétéroalcynyle en C_2-C_6, ou $NR_{51}R_{52}$, où R_{51} et R_{52} chacun indépendamment sont un alkyle, alcényle ou alcynyle en C_2-C_{10}, hétéroalkyle, hétéroalcényle ou hétéroalcynyle, un arylalkyle, arylalcényle ou arylalcynyle en C_7-C_{15}, ou hétéroarylalkyle, hétéroarylalcényle ou hétéroarylalcynyle, un acyle en C_3-C_{10}, dans la mesure où seul un de R_{51} ou R_{52} peut être acyle ou R_{51} et R_{52} pris conjointement sont cycloalkyle, cycloalcényle ou cycloalcynyle en C_3-C_6;

R_{65} est l'hydrogène, un alkyle, alcényle ou alcynyle en C_1-C_2, ou OR_{66}, où R_{66} est un alkyle, alcényle ou alcynyle en C_1-C_2;

R_{67} est un alkyle, alcényle ou alcynyle en C_4-C_{10}, hétéroalkyle, hétéroalcényle ou hétéroalcynyle, aryle, hétéroaryle, un arylalkyle, arylalcényle ou arylalcynyle en C_7-C_{15} ou hétéroarylalkyle, hétéroarylalcényle ou hétéroarylalcynyle, $NR_{51}R_{52}$, ou OR_{68}, où R_{51} et R_{52} ont les définitions décrites ci-dessus et où R_{68} est un alkyle, alcényle ou alcynyle en C_3-C_{10}; hétéroalkyle, hétéroalcényle ou hétéroalcynyle, aryle, hétéroaryle, ou un arylalkyle, arylalcényle ou arylalcynyle en C_7-C_{15} ou hétéroralylalkyle, hétéroarylalcényle ou hétéroarylalcynyle ;

les lignes discontinues dans les structures représentent les doubles liaisons facultatives, à condition, toutefois, que les doubles liaisons ne soient pas contiguës et à condition, de surcroît, que lorsque ces doubles liaisons existent, les configurations de substitution autour de ces liaisons ne puissent alors transgresser la valence de double liaison ; et

les lignes sinueuses représentent la géométrie oléfine qui est soit *cis* (Z) ou *trans* (E), et sauf indication contraire pour les substituants R_{40} jusqu'à R_{68}, tous les isomères géométriques oléfines (c'est-à-dire *cis* (Z) ou *trans* (E)) des composants ci-dessus sont inclus.

2. Composé selon la revendication 1, dans lequel le composé est un modulateur de RXR sélectif pour les dimères.

3. Composé selon la revendication 2, dans lequel le composé est efficace pour moduler les interactions des homodimères RXR.

4. Composé selon la revendication 3, dans lequel le composé est un antagoniste d'homodimère RXR.

5. Composé selon la revendication 2, dans lequel le composé est efficace pour moduler les interactions des homodimères RXR, et dans lequel l'hétérodimère RXR comprend un RXR complexé avec un autre récepteur intracellulaire qui forme un hétérodimère avec RXR.

6. Composé selon la revendication 5, dans lequel le composé est un antagoniste d'hétérodimère RXR.

7. Composé selon la revendication 5, dans lequel RXR est choisi dans le groupe consistant en RXRα, RXRβ et RXRγ.

8. Composé selon la revendication 5, dans lequel l'autre récepteur intracellulaire est choisi dans le groupe consistant en PPARα, PPARβ, PPARγ1, PPARγ2, TRα, TRβ, VDRs, RARα, RARβ, RARγ, NGFIBs, NURR1s, LXRα, LXRβ et DAXs.

9. Composé selon la revendication 2, dans lequel le composé est efficace pour traiter les maladies et conditions liées à la peau, les conditions cancéreuses et précancéreuses, les maladies de l'oeil, les maladies cardiovasculaires, les troubles du métabolisme, l'obésité, les maladies inflammatoires, les maladies neurodégénérescentes, les maladies impliquant la modulation de l'apoptose, les maladies impliquant la modulation de la prolifération cellulaire, les maladies impliquant la modulation de la différenciation cellulaire, les maladies du système immunitaire, un dysfonctionnement hypophysaire, les maladies impliquant le virus du papillome humain, la cicatrisation des plaies ou le rétablissement de la croissance du système pileux.

10. Composé selon la revendication 9, dans lequel le composé est efficace pour traiter le diabète sucré non insulinodépendant et le diabète sucré insulinodépendant.

11. Composé selon la revendication 2, choisi dans le groupe consistant en acide (2E, 4E, 6E)-7-(3,5-diisopropyl-2-n-heptyloxyphényl)-3-méthylocta-2,4,6-triénoïque (composé 146); l'acide (2E, 4E, 6Z)-7-(3,5-diisopropyl-2-n-heptyloxyphényl)-3-méthylocta-2,4,6-triénoïque (composé 147); l'acide (2E, 4E,)-7-(3,5-diisopropyl-2-n-heptyloxyphényl)-3-méthylocta-2,4-diénoïque (composé 148); l'acide (2Z, 4E,)-7-(3,5-diisopropyl-2-n-heptyloxyphényl)-3-méthylocta-2,4-diénoïque (composé 149); l'acide (2E, 4E, 6E)-7-(3,5-diisopropyl-2-n-benzyloxyphényl)-3-méthylocta-2,4,6-triénoïque (composé 150); l'acide (2E, 4E, 6E)-7-(3,5-diisopropyl-2-n-butyloxyphényl)-3-méthylocta-2,4,6-triénoïque (composé 151).

12. Composition pharmaceutique comprenant une quantité pharmaceutiquement efficace d'un composé selon la re-

vendication 2 et une substance support pharmaceutiquement acceptable.

13. Composition pharmaceutique selon la revendication 12, dans laquelle la composition est formulée pour l'administration orale, topique, intraveineuse, par suppositoire ou voie parentérale.

14. Composition pharmaceutique selon la revendication 13, dans laquelle la composition est efficace pour traiter les conditions et maladies liées à la peau, les conditions cancéreuses et précancéreuses, les maladies de l'oeil, les maladies cardiovasculaires, les troubles du métabolisme, l'obésité, les maladies inflammatoires, les maladies neurodégénérescentes, les maladies impliquant une modulation de l'apoptose, les maladies impliquant la modulation de prolifération cellulaire, les maladies impliquant la modulation de la différenciation cellulaire, les maladies du système immunitaire, le dysfonctionnement hypophysaire, les maladies impliquant le virus du papillome humain, la cicatrisation des plaies ou le rétablissement de la croissance du système pileux.

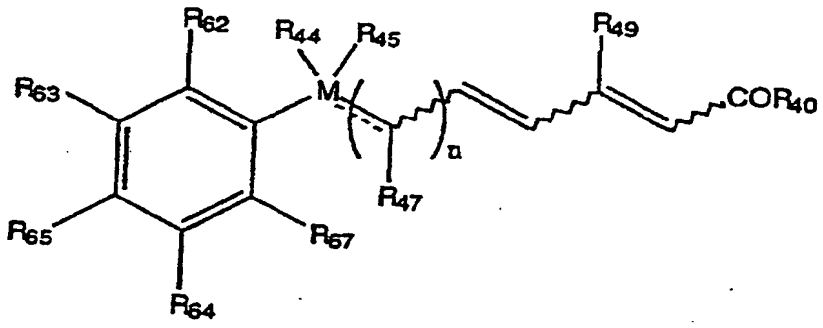
15. Composition selon la revendication 14, dans laquelle le composé est efficace pour traiter le diabète sucré non insulinodépendant et le diabète sucré insulinodépendant.

16. Composition pharmaceutique selon la revendication 12, dans laquelle la composition est administrée à un patient en tant que dose unitaire allant de 1µg/kg de poids corporel jusqu'à environ 500 mg/kg de poids corporel.

17. Composition pharmaceutique selon la revendication 12, dans laquelle la composition est administrée à un patient en tant que dose unitaire allant d'environ 10 µg/kg de poids corporel jusqu'à environ 250 mg/kg de poids corporel.

18. Composition pharmaceutique selon la revendication 12, dans laquelle la composition est administrée à un patient en tant que dose unitaire allant d'environ 20 µg/kg de poids corporel jusqu'à environ 100 mg/kg de poids corporel.

19. Utilisation d'un composé modulateur de RXR sélectif pour les dimères, de formule:



(IV)

telle que définie dans la revendication 1 ;
pour la préparation d'un médicament pour moduler des processus qui sont à médiation par des homodimères RXR et/ou des hétérodimères RXR, en administrant à un patient une quantité efficace dudit composé.

20. Utilisation selon la revendication 19, dans laquelle le processus est un processus à médiation par des homodimères RXR.

21. Utilisation selon la revendication 19, dans laquelle le processus est un processus à médiation par des hétérodimères RXR.

22. Utilisation selon la revendication 19, dans laquelle le processus est choisi dans le groupe consistant en des conditions et maladies liées à la peau, des conditions cancéreuses et précancéreuses, les maladies de l'oeil, maladies cardiovasculaires, des troubles du métabolisme, obésité, les maladies inflammatoires, les maladies neurodégénérescentes, les maladies impliquant la modulation de l'apoptose, la modulation des maladies impliquant la pro-

lifération cellulaire, la modulation des maladies impliquant la différenciation cellulaire, les maladies du système immunitaire, le dysfonctionnement hypophysaire, les maladies impliquant le virus du papillome humain, la cicatrisation des plaies et le rétablissement de la croissance du système pileux.

23. Utilisation selon la revendication 22, dans laquelle le processus de trouble du métabolisme est sélectionné dans le groupe constitué par le diabète sucré non insulinodépendant et le diabète sucré insulinodépendant.

24. Utilisation selon la revendication 19, dans laquelle le composé modulateur de RXR sélectif pour les dimères est combiné à une substance suppport pharmaceutiquement acceptable pour former une composition pharmaceutique.

25. Utilisation selon la revendication 24, dans laquelle la composition pharmaceutique est formulée pour l'administration orale, topique, intraveineuse, par suppositoire ou par voie parentérale.

26. Utilisation selon la revendication 24, dans laquelle la composition pharmaceutique est efficace pour traiter les processus choisis dans le groupe consistant en conditions et maladies liées à la peau, les conditions cancéreuses et précancéreuses, les maladies de l'oeil, les maladies cardiovasculaires, les troubles du métabolisme, l'obésité, les maladies inflammatoires, les maladies neurodégénérescentes, les maladies impliquant la modulation de l'apoptose, les maladies impliquant la modulation de la prolifération cellulaire, les maladies impliquant la modulation de la différenciation cellulaire, les maladies du système immunitaire, le dysfonctionnement hypophysaire, les maladies impliquant le virus du papillome humain, la cicatrisation des plaies et le rétablissement de la croissance du système pileux.

27. Utilisation selon la revendication 26, dans laquelle le processus de trouble du métabolisme est choisi dans le groupe constitué par le diabète sucré non insulinodépendant et le diabète sucré insulinodépendant.

28. Utilisation selon la revendication 24, dans laquelle la composition est administrée à un patient en tant que dose unitaire allant d'environ 1 µg/kg de poids corporel jusqu'à environ 500 mg/kg de poids corporel.

29. Utilisation selon la revendication 24, dans laquelle la composition est administrée à un patient en tant que dose unitaire allant d'environ 10 µg/kg de poids corporel jusqu'à environ 250 mg/kg de poids corporel.

30. Utilisation selon la revendication 24, dans laquelle la composition est administrée à un patient en tant que dose unitaire allant d'environ 20 µg/kg de poids corporel jusqu'à environ 100 mg/kg de poids corporel.